Selective Sequential Intramolecular Cyclization of Ethenetricarboxylates with Arylpropenamines

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Hirotaka Sugiura

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Preface

This thesis deals with the studies conducted during April 2016 to March 2019 under the guidance of Professor Akiya Ogawa at the Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University.

This thesis is concerned with the studies on the highly selective intramolecular cyclization reaction of ethenetricarboxylate and other electron-deficient carboxylic acids with arylpropenamines. One of the topics is the control of the chemo- and stereoselectivity of the intramolecular cyclization reaction by phenylpropenamines bearing substituents on the benzene ring. The other is stereoselective sequential intramolecular cyclization reactions of ethenetricarboxylates with heteroarylpropenamines. In the course of the research, novel chemoselective intramolecular cyclization reactions of β-substituted cinnamylamines are also studied.

Department of Applied Chemistry

Graduate School of Engineering

Osaka Prefecture University

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Hirotaka Sugiura

# Contents

Chapter 1

General Introduction

Multicyclic compounds are present in a large number of physiologically active substances and functional materials. Among them, multicyclic heterocycles containing nitrogen and oxygen often have high functionality, and it is important to develop efficient synthesis methods of the heterocycles.[1] Their preparation usually requires lengthy steps. It is desirable to construct such multicyclic compounds rapidly with high efficiency.

Cycloaddition reactions form two bonds in cyclic systems. Intramolecular reactions access fused and bridged ring systems.[2] Intramolecular cycloaddition reactions of styrenes may form [2 + 2] [3] and [4 + 2] [4] cycloadducts.

However, [4 + 2] cycloaddition (Diels-Alder) reaction of the styrene as a diene, requires relatively high temperature, because it involves dearomatization of the benzene ring. [5] Intramolecular Diels-Alder (IMDA) reaction of vinylfuran as a diene has been reported. But it generally requires higher temperatures than that of a furan ring as a diene[6], and there are fewer examples.

Yamazaki's group reported that Lewis acid (MX_n)-promoted cyclization/halogenation of alkenyl ethenetricarboxylates gives 3,4-*trans* five-membered rings stereoselectively with high generality ((**a**) in Scheme 1-1).[7] 2-Alkenyl amides of ethenetricarboxylates also undergo facile intramolecular ene reactions ((**b**) in Scheme 1-1).[7c] Ethenetricarboxylate derivative has high electrophilicity at the alkene site by three carbonyl groups.[8] The utility of ethentricarboxylates has been shown for various inter- and intramolecular reactions, for example, leading to cyclic compounds. It is of interest to examine the reaction of highly electrophilic ethenetricarboxylates bearing arylvinyl groups.

In this thesis, sequential amide formation/cyclization reactions of ethenetricarboxylate and other electron-deficient alkenic carboxylate, such as fumarate have been investigated. The selectivity of the reactions has been discussed.
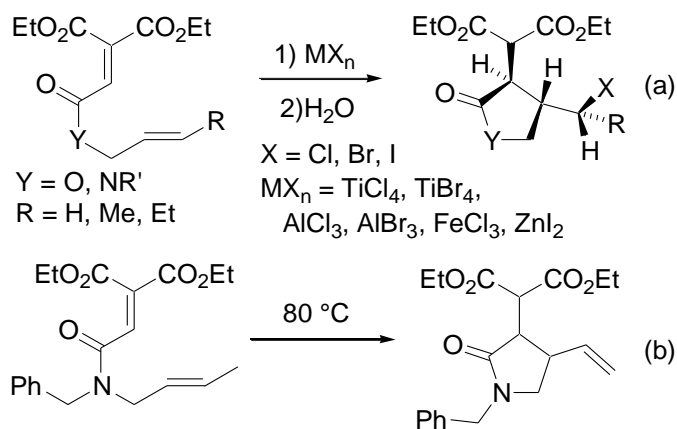
Scheme 1-1. Cyclization reaction of ethenetricarboxylate derivatives.[7]

This thesis is divided into seven chapters. The introduction is presented in chapter 1.

In chapter 2, IMDA reaction of 2-furylmethylamides of ethenetricarboxylate in sequential process is described. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and 2-furylmethylamines in the presence of EDCI/HOBt/Et$_3$N at room temperature led directly to IMDA adducts.
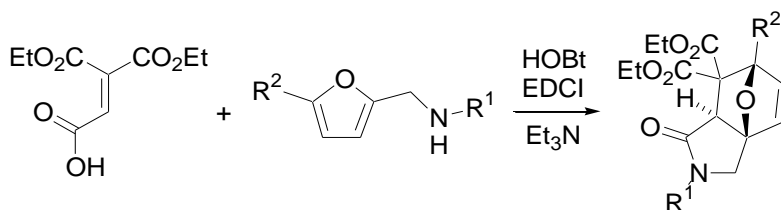
Scheme 1-2. Chapter 2.

In chapter 3, intramolecular [2 + 2] and [4 + 2] cycloaddition reactions of cinnamylamides of ethenetricarboxylate in sequential processes are described. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and *trans*-cinnamylamines in the presence of

EDCI/HOBt/Et₃N led to pyrrolidine products in one pot via intramolecular [2 + 2] and [4 + 2] cycloaddition reactions. The types of the products depend on the substituents on the benzene ring and the reaction conditions. Reaction of cinnamylamines without substituents on the benzene ring and with halogens and OMe on the *para* position at room temperature gave cyclobutane-fused pyrrolidines as the major products via [2 + 2] cycloaddition. On the other hand, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and cinnamylamines bearing electron-withdrawing groups such as NO₂, CN, CO₂Me, CO₂Et, and CF₃ on *ortho* and *para* positions in the presence of EDCI/HOBt/Et₃N at room temperature or at 60−80 °C gave tetrahydrobenz[*f*]isoindolines via [4 + 2] cycloaddition (IMDA) as the major products.
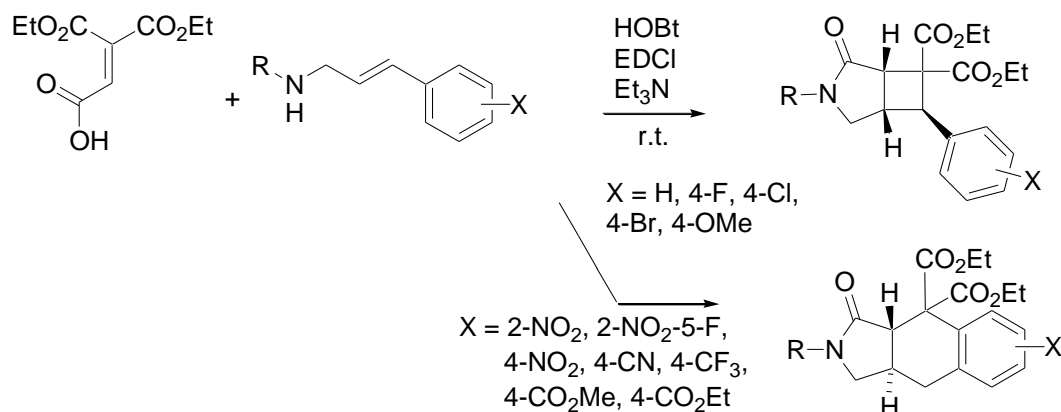
Scheme 1-3. Chapter 3.

In chapter 4, IMDA reactions of various 3,3-diarylpropenylamides of electron-deficient alkenes to give hexahydrobenzo[*f*]isoindoles were investigated. Reaction of ethenetricarboxylate with 3,3-diaryl-2-propen-1-amines under the amide formation conditions gave the tricyclic compounds in sequential processes involving IMDA reaction. The reaction gave *cis*- and *trans*-fused tricyclic compounds selectively, depending on the substituents on the benzene ring, reaction temperature and solvent. In the reaction with 1,1-diethyl 2-hydrogen ethenetricarboxylate substituted by 3,3-diaryl-2-propen-1-amines, *trans*-substituted aryl group reacted mainly as a styrene component. Amides of electron-deficient alkenic carboxylic acids

such as fumarate do not undergo cyclization at room temperature sequentially and the reaction on heating gave *trans*-fused hexahydrobenzo[*f*]isoindoles.
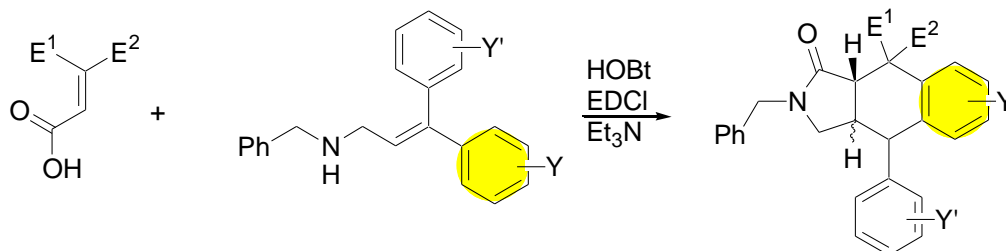
Scheme 1-4. Chapter 4.

In chapter 5, the stereoselectivity in the reaction of ethenetricarboxylate with heteroarylpropenylamines was investigated. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with (*E*)-3-(2-furyl)-2-propenylamines in the presence of EDCl/HOBt/Et$_3$N at 80-110 °C gave *cis*-fused tricyclic compounds as the major products. On the other hand, reaction with (*E*)-3-(3-furyl)-2-propenylamines at 80-110 °C gave *trans*-fused tricyclic compounds as the major products. The reaction with *E*-3- and 4-pyridinyl-2-propenyl-amines was also carried out. The reaction with 3-pyridinyl propenylamine gave HOBt-incroporated pyrrolidine diastereoselectively, and the reaction with 4-pyridinyl-2-propenylamines gave a complex mixture.
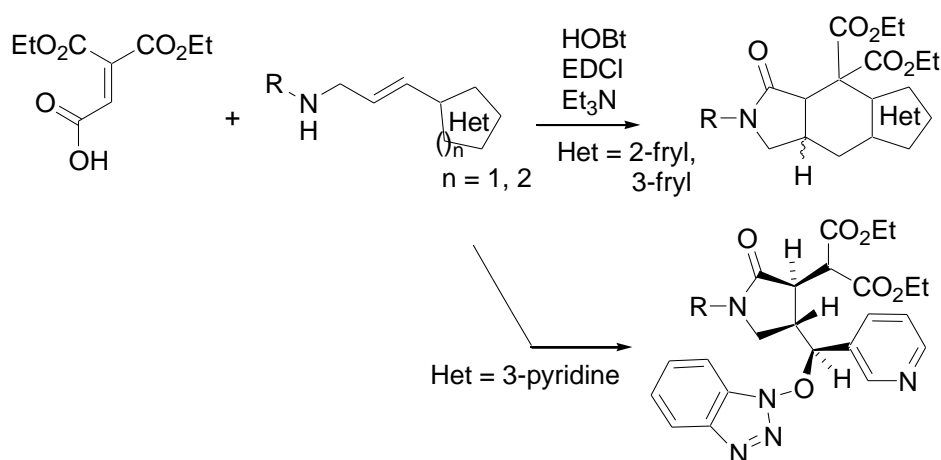
Scheme 1-5. Chapter 5.

In chapter 6, reaction of *β*-substituted cinnnamylamines of ethenetricarboxylates was examined. Reaction of ethenetricarboxylate with (*E*)-3-aryl-2-buten-1-amine and (*E*)-3-aryl-3-bromo-2-propen-1-amine under the amide formation conditions gave cyclized products with chemo- and stereoselectivites, similar to that with cinnamylamines in chapter 3 (Scheme 1-6).

Finally, the summary of this thesis is presented in chapter 7.
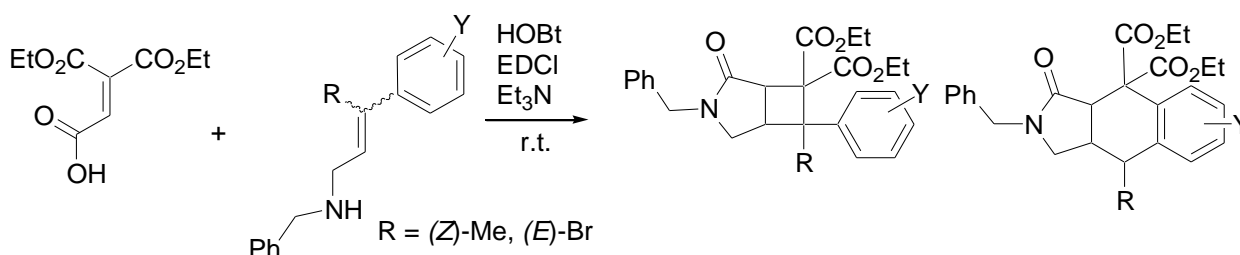
Scheme 1-6. Chapter 6.

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Chapter 2

Sequential Intramolecular Diels-Alder Reaction of Furylamines with Ethenetricarboxylate

2-1 Introduction

Intramolecular Diels-Alder (IMDA) reaction is one of the most widely used synthetic tools for natural products.[1]

The IMDA reaction of furans as diene is used for facile formation of multicyclic skeletons. [2] In normal electron-demand Diels-Alder reaction, the alkene component (dienophile) is usually electron-deficient. In general, the greater number of electron-withdrawing substituents on the double bond, results in higher reactivity of the dienophile, owing to the lowering of the energy of the LUMO of the dienophile by the substituents. Ethenetricarboxylate derivatives bearing three carbonyl groups have been employed as highly electrophilic C=C components in various bond-forming reactions.[3] Although an intramolecular inverse electron demand hetero Diels-Alder reaction of 1-allylic 2,2-dimethyl esters of ethene-1,2,2-tricarboxylate has been studied,[4] only a few normal electron demand Diels-Alder reactions of ethenetricarboxylate related compounds as electron-deficient dienophiles have been reported.[5] Ethenetricarboxylates allow for the facile derivatization at 2-carboxyl group. The electron-deficient alkene moiety is expected to work as a reactive dienophile in the IMDA reaction.

In this chapter, sequential IMDA reaction of ethenetricarboxylate derivatives with furan as diene has been studied.

2-2 Results and Discussion

IMDA reaction of ethenetricarboxylates has been examined. Reaction of *N*-allyl- or *N*-benzyl-2-furylmethylamine **2a,c** and 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** in the presence of EDCI/HOBt/Et$_3$N at room temperature led directly to an IMDA adducts **3a,c** in 65-82% yields (Table 2-1).[6] The possible intermediate **4** could not be observed under the reaction conditions of amide formation (Scheme 2-1). The reaction of **1** and **2a** in the absence of condensation reagents only gave the mixture of **1** and **2a**, probably forming a salt. Treatment of the mixture with condensation reagents led to the Diels-Alder adduct **3a** in 75% yield.

Table 2-1. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and 2-furylmethylamines **2**.
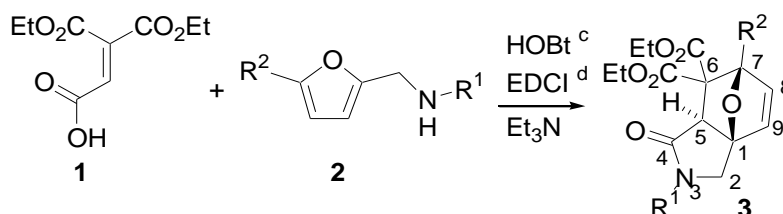
Entry	2	R^1	R^2	Temp, Time	Solvent	Product	Yield (%)
1 [a]	**2a**	CH$_2$CH=CH$_2$	H	r.t., 17 h	THF	**3a**	82
2 [a]	**2b**	CHMePh	H	r.t., 20 h	THF	**3b**	43(dr=1:1)
3 [a]	**2c**	CH$_2$Ph	H	r.t., 21 h	THF	**3c**	65
4	**2c**	CH$_2$Ph	H	60 °C, 20 h	THF	**3c**	46
5	**2c**	CH$_2$Ph	H	80 °C, 20 h	CH$_2$ClCH$_2$Cl[b]	**3c**	50
6	**2d**	CH$_2$Ph	Br	r.t., 20 h	THF	**3d**	48
7	**2d**	CH$_2$Ph	Br	r.t., 1 h	THF	**3d**	40
8	**2d**	CH$_2$Ph	Br	60 °C, 20 h	THF	**3d**	55
9	**2d**	CH$_2$Ph	Br	80 °C, 20 h	CH$_2$ClCH$_2$Cl[b]	**3d**	75

[a] Results of entries 1-3 are cited from reference 6. [b] The byproducts were removed by column chromatography.[7] [c] HOBt: 1-hydroxybenzotriazole. [d] EDCI: 1-[3-(dimethyl-amino)propyl]-3-ethylcarbodiimide hydrochlorid.
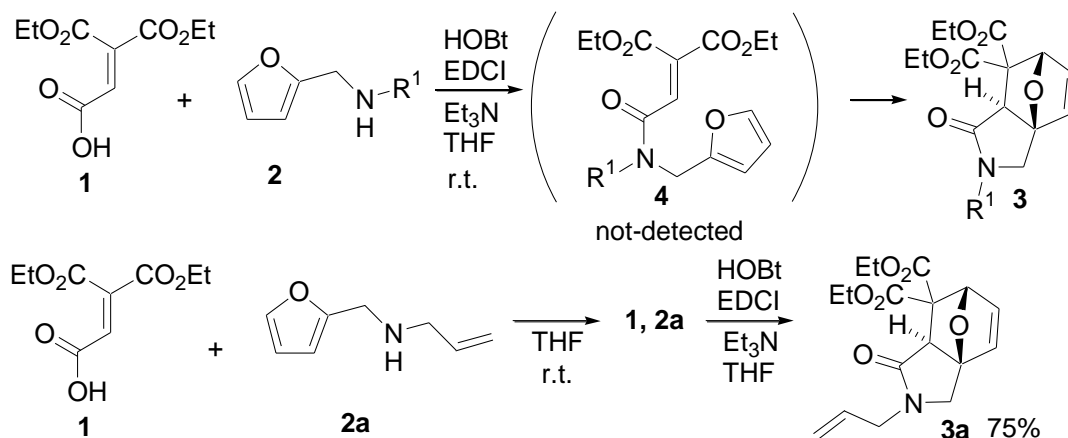
Scheme 2-1. Formation of IMDA product **3**.

The structure of 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-ene **3a** was determined by X-ray analysis (Figure 2-1). The exo stereochemistry of Diels-Alder adducts **3a-d** with respect to the amide group was also determined by NOEs. NOEs between C5-*H* and C2-H*H* and/or between C5-*H* and C9-*H* were observed (atom numbering is shown in Table 2-1).
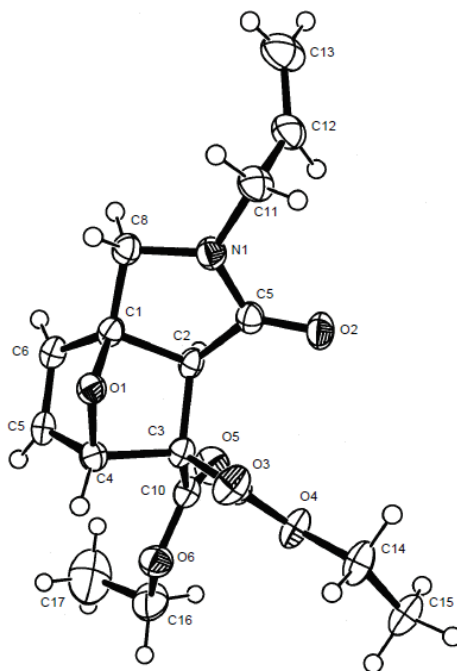
Figure 2-1. ORTEP drawing of **3a** (thermal ellipsoids are drawn at 50% probability). The atom numbering is different from that in Table 2-1.

In order to explain the stereoselectivity of the IMDA reaction was examined by B3LYP/6-31G* calculations including the PCM solvent effect (solvent=THF).

The endo and exo IMDA reactions from a model compound **4m** as a possible intermediate were calculated (Figure 2-2). The activation energy $\Delta G^{\ddagger}$ of endo TS (31.17 kcal/mol) is much higher than that of exo TS (21.41 kcal/mol).
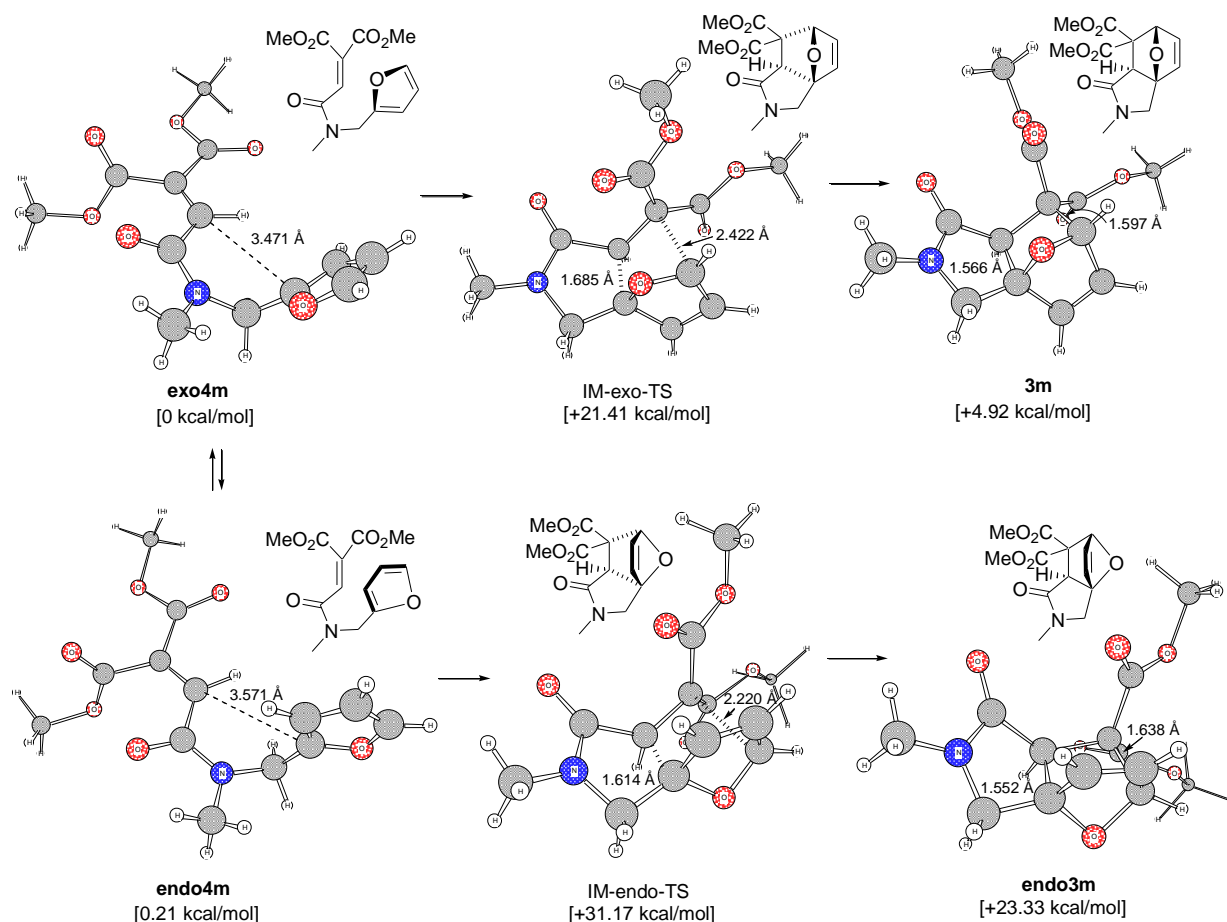
Figure 2-2. RB3LYP/6-31G* SCRF = (PCM, solvent=THF) optimized structures for endo:exo IMDA reaction paths of **4m**.

The acid-catalyzed IMDA reactions of **4m** were also calculated (Figure 2-3). The protonated six-membered ring intermediates with hydrogen bonding were assumed.[8] The acid *in situ*, possibly generating from EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

hydrochloride) or starting material **1** may catalyze the cycloaddition reactions. Stepwise mechanism with zwitter-ionic intermediates was obtained for the H^+-catalyzed reaction. The acid-catalyzed reaction lowers the activation energies compared to the uncatalyzed reaction. The activation energy $\Delta G^{\ddagger}$ of the second bond formation TS (H^+IM-exo-TS2) (10.10 kcal/mol) is higher than that of the first TS (H^+IM-exo-TS1) (1.51 kcal/mol) for exo addition. The H^+-catalyzed process accelerates the formation of the exo adduct **3**.

The first bond formation TS (H^+IM-endo-TS1) for endo addition was obtained; however the second bond formation TS could not be obtained. Optimization of the initial structure of endo**4m-H$^+$** led to the intermediate (H^+IM- endo-Int). The endo TS and product are highly unstable probably because of the steric constraint. Therefore, the exo adducts **3** are produced stereoselectively.

Reaction of 1-phenylethyl-2-furylmethylamine or **2b** gave Diels-Alder adducts **3b** with diastereomer ratios of 1:1 in 43% yield. Reaction of *N*-benzyl-(5-bromofuran-2-yl)methylamine **2d** gave Diels-Alder adduct **3d** at room temperature in THF for 1 h in 40%, for 20 h in 48% and at 80 °C in CH_2ClCH_2Cl[7] for 20 h in 75%. A small amount of byproducts formed at room temperature possibly contain amine adducts at C=C bond. The reaction of **1** and **2c** with DCC gave a complex mixture containing a small amount of DCU-incorporated byproducts.[9]
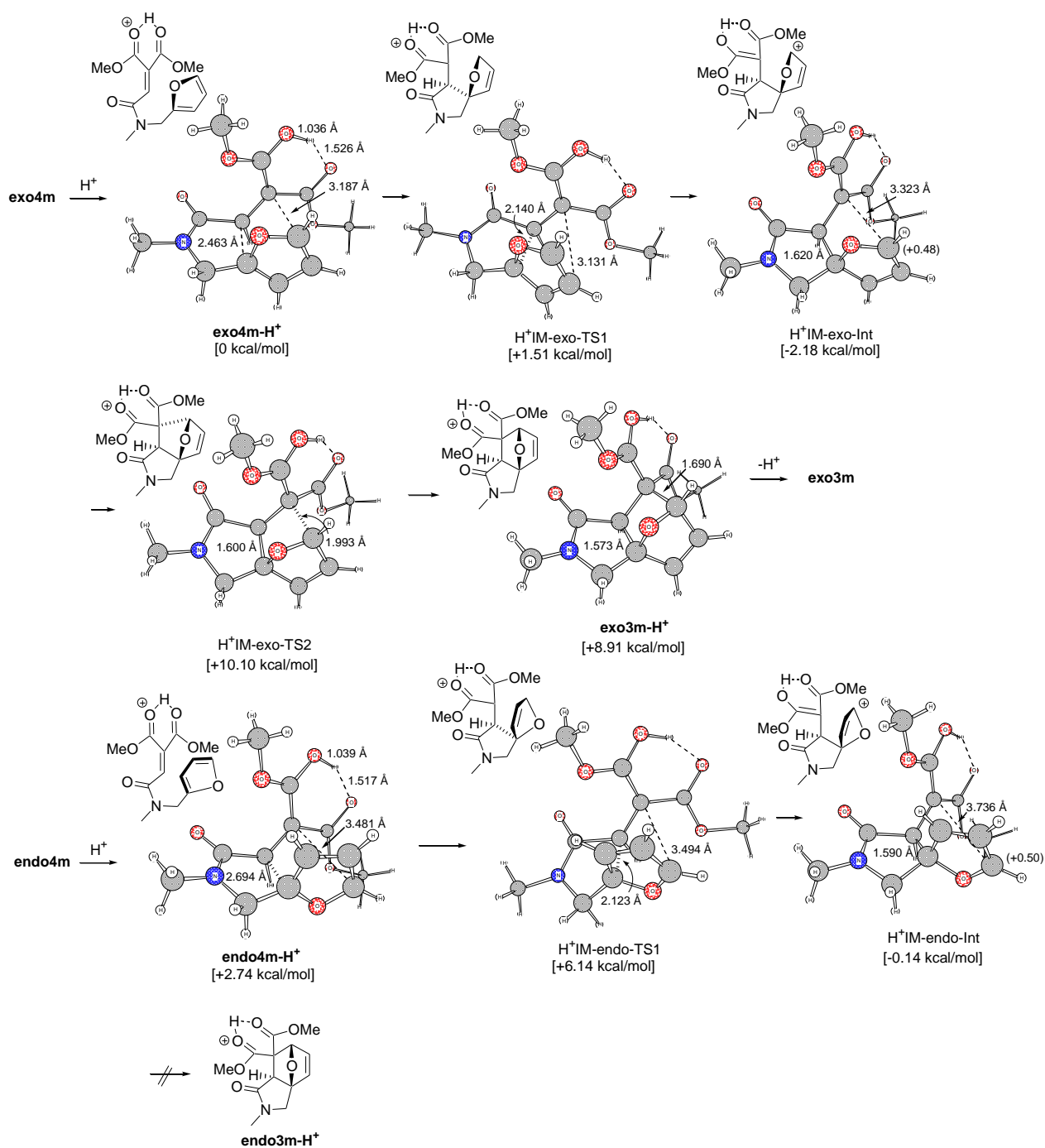
Figure 2-3. RB3LYP/6-31G* SCRF = (PCM, solvent=THF) optimized structures for endo:exo acid-catalyzed IMDA reaction paths of **4m**. Values in parentheses are Mulliken charges with hydrogens summed into heavy atoms.

2-3 Conclusion

In summary, IMDA reaction of ethenetricarboxylate and furylamines has been studied. Reaction of benzyl- or allyl-2-furylmethylamine and 1,1-diethyl 2-hydrogen ethenetricarboxylate in the presence of EDCI/HOBt/Et$_3$N at room temperature led directly to IMDA adducts stereoselectively. The highly functionalized cyclic compounds obtained in this chapter should be useful synthetic intermediates.

2-4 Experimental Section

General Procedures

[1]H Chemical shifts are reported in ppm relative to Me$_4$Si. [13]C Chemical shifts are reported in ppm relative to CDCl$_3$ (77.1 ppm). [13]C mutiplicities were determined by DEPT and HSQC. Peak assignments are made by 2D COSY, HSQC, NOESY, and HMBC spectra. Mass analyzer type used for EI is double-focusing in the HRMS measurements. Column chromatography was performed on silica gel (75-150 μm).

***N*-Benzyl-furfurylamine (2c)**: (8.9 mmol scale, 1.62 g, 97%). **2c** was also prepared by reaction of furfurylamine (2 equiv) with benzyl bromide in Et$_2$O (5.0 mmol scale, 449 mg, 47%) according to the literature procedure.[10]

2c: R$_f$ = 0.2 (hexane-Et$_2$O = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.85 (bs, 1H), 3.78 (s, 4H), 6.18 (bd, J = 3.3 Hz, 1H), 6.31 (dd, J = 3.3, 1.8 Hz, 1H), 7.22-7.28 (m, 1H), 7.29-7.34 (m, 4H), 7.36 (dd, J = 1.8, 0.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 45.37 (CH$_2$), 52.81 (CH2), 107.12 (CH), 110.15 (CH), 127.08 (CH), 128.32 (CH), 128.46 (CH), 139.86 (C), 141.88 (CH), 153.80 (C).

***N*-Benzyl-(5-bromofuran-2-yl)methylamine (2d)**: (9.0 mmol scale, 2.14 g, 89%): R$_f$ = 0.3 (hexane-Et$_2$O = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.75 (bs, 1H), 3.71 (s, 2H), 3.75 (s, 2H), 6.13 (d, J = 3.2 Hz, 1H), 6.20 (d, J = 3.2 Hz, 1H), 7.21-7.26 (m, 1H),

7.28-7.33 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 45.28 (CH$_2$), 52.60 (CH$_2$), 109.86 (CH), 111.72 (CH), 120.57 (C), 127.06 (CH), 128.20 (CH), 128.41 (CH), 139.62 (C), 155.94 (C); IR (neat) 3329, 3027, 2917, 2830, 1602, 1505, 1453, 1200, 1125, 1010 cm^{-1}; MS (EI) m/z 267 (M$^+$, 12), 265 (M$^+$, 12), 186 (11), 161 (21), 159 (22), 106 (23), 91 (100%); HRMS (EI) M$^+$ 265.0099, 267.0045 (calcd for C$_{12}$H$_{12}$BrNO 265.0102, 267.0082).

Typical experimental procedure preparation of 3 in Scheme 1 (Table 1, entry 4). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (272 mg, 1.00 mmol) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate[11] upon treatment with CF$_3$CO$_2$H)[12] in THF (0.8 mL) were added *N*-benzyl-furfurylamine (**2c**) (385 mg, 1.00 mmol) in THF (1.5 mL), Et$_3$N (0.14 mL, 101 mg, 1.00 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2.00 mmol), and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to 60 °C and then stirred for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **3c** (175 mg, 46%).

3c: (2.35 mmol scale, 590 mg, 65%): R$_f$ = 0.8 (CH$_2$Cl$_2$-Et$_2$O = 1 : 1); colorless crystals; mp 138-140 °C (EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 3.47 (s, 1H), 3.59 (d, J = 11.9 Hz, 1H), 3.65 (d, J = 11.9 Hz, 1H), 4.11-4.40 (m, 5H), 4.68 (d, J = 15.0 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 6.32 (dd, J = 5.7, 1.6 Hz, 1H), 6.54 (d, J = 5.7 Hz, 1H), 7.23-7.36 (m, 5H). Selected NOEs are between δ 3.47 (C5-H) and δ 3.65 (C2-HH), 6.54 (C9-H), between δ 3.65 (C2-HH) and δ 3.47 (C5-H), and between δ 6.32 (C8-H) and δ 5.37 (C7-H), 6.54 (C9-H).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.07 (CH$_3$), 14.09 (CH$_3$), 46.76

(CH$_2$), 48.13 (CH$_2$), 54.69 (CH), 61.99 (CH$_2$), 62.23 (CH$_2$), 62.38 (CH$_2$), 83.58 (CH), 89.49 (C), 127.74 (CH), 128.00 (CH), 128.88 (CH), 135.73 (CH), 135.89 (CH), 136.96 (CH), 168.20 (C), 168.86 (C), 170.01 (C). Selected HMBC correlations are between δ 3.59 (C2-HH), 3.65 (C2-HH), 5.37 (C7-H) and δ 136.96 (C9), between δ 3.59 (C2-HH), 6.54 (C9-H), 5.37 (C7-H), 6.32 (C8-H) and δ 89.49 (C1) and between δ 3.47 (C5-H), 6.54 (C9-H), 6.32 (C8-H) and δ 83.58 (C7).; IR (KBr) 2984, 1756, 1734, 1690, 1478, 1368, 1266, 1192, 1117, 1046 cm^{-1}; MS (EI) m/z 385 (M$^+$, 1.9), 340 (9.4), 295 (11), 248 (19), 221 (25), 200 (40), 186 (100%); HRMS (EI) 385.1521 (calcd for C$_{21}$H$_{23}$NO$_6$ M$^+$ 385.1525); Anal. Calcd for C$_{21}$H$_{23}$NO$_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.50; H, 6.06; N, 3.76.

3d: (1 mmol scale, 227 mg, 48%): R$_f$ = 0.1 (hexane-Et$_2$O = 1 : 4); pale yellow crystals; mp 127-127.5 °C (EtOAc-Et$_2$O = 1 : 1); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 3.54 (s, 1H), 3.66 (d, J = 11.9 Hz, 1H), 3.78 (d, J = 11.9 Hz, 1H), 4.24-4.41 (m, 4H), 4.43 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 6.41 (d, J = 5.5 Hz, 1H), 6.54 (d, J = 5.5 Hz, 1H), 7.25-7.30 (m, 3H), 7.33-7.37 (m, 2H). Selected NOEs are between δ 3.54 (C5-H) and δ 6.54 (C9-H), between δ 3.78 (C2-HH) and δ 6.54 (C9-H), and between δ 6.41 (C8-H) and δ 6.54 (C9-H).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.96 (CH$_3$), 14.05 (CH$_3$), 46.77 (CH$_2$), 48.09 (CH$_2$), 57.80 (CH), 62.42 (CH$_2$), 62.56 (CH$_2$), 66.86 (C), 87.69 (C), 91.14 (C), 127.86 (CH), 128.02 (CH), 128.94 (CH), 135.50 (C), 137.23 (CH), 140.81 (CH), 166.06 (C), 167.52 (C), 169.23 (C). Selected HMBC correlations are between δ 3.78 (C2-HH) and δ 137.23 (C9), between δ 3.66 (C2-HH), 6.54 (C9-H), 6.41 (C8-H) and δ 87.69 (C1) and between δ 3.54 (C5-H), 6.54 (C9-H), 6.41 (C8-H) and δ 91.14 (C7).; IR (KBr) 2980, 1745, 1718, 1687, 1475, 1440, 1359, 1311, 1288, 1264, 1240, 1213, 1199, 1083, 1037 cm^{-1}; MS (EI) m/z 465 (M$^+$, 0.6), 463 (M$^+$, 0.6), 438 (4.5), 436 (4.6), 266 (92), 264 (100%); HRMS (EI) 463.0648, 465.0623 (calcd for C$_{21}$H$_{22}$BrNO$_6$ M$^+$ 463.0631, 465.0610); Anal. Calcd for C$_{21}$H$_{22}$BrNO$_6$: C, 54.32; H, 4.78; N, 3.02. Found: C, 54.22; H, 4.68; N, 3.05.

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Chapter 3

Intramolecular [2 + 2] and [4 + 2] Cycloaddition Reactions of Cinnamylamides of Ethenetricarboxylate in Sequential Processes

3-1 Introduction

Multiple bond formations in one pot are efficient to synthesize cyclic compounds. Intramolecular cycloaddition reactions in cinnamyl group (styrenes) give [2 + 2] and [4 + 2] cycloadducts.[1, 3b]

Intramoramolecuar Diels-Alder (IMDA) reaction between styryl group as dienes and alkynes were reported can be to give tricyclic compounds.[2] One the other hand, alkenes bearing styryl group to undergoing [2 + 2] cycloaddition give cyclobutane-fused compounds by photochemical[1] or metal-catalyzed reaction.[3] Snider et al. reported that heating cinnamyl ester of ethentricarboxylate led to an equilibrium mixture of the ester and a hetero Diels-Alder adduct.[4] Thus, styrene works as an alkene or diene component in intramolecular [2 + 2] or [4 + 2] cycloadditions with electron-deficient alkenes. The both reactions may be useful for the construction of multicyclic skeletons and the question is how to control the selectivity.

Ethenetricarboxylate derivatives have been employed as highly electrophilic C=C components in various bond-forming reactions.[5] In chapter 2, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and 2-furylmethylamines in the presence of EDCI/HOBt/Et$_3$N at room temperature led directly to IMDA adducts in one pot.[6]
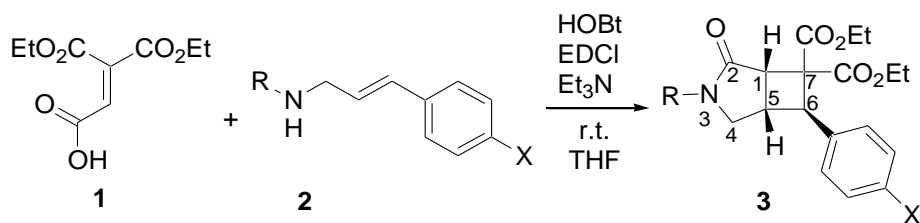
It is of interest to investigate the reaction of the highly electrophilic ethenetricarboxylates bearing styryl group as an extension of an alkenyl group. In this chapter, the reaction of cinnamyl amides bearing electron-donating groups and electron

withdrawing-groups on the benzene ring has been examined. Development of selective intramolecular cyclization of styrenes and elucidation the factor to control the selectivity.

3-2 Result and Discussion

First, reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and *E*-cinnamylamines (X = H) **2a** in the presence of EDCI/HOBt/Et$_3$N have been examined. It was found that the reaction gave cyclobutane-fused pyrrolidines **3a** in 43% yield as the isolable major product (Table 3-1). The products may be formed via amide formation/intramolecular [2 + 2] cycloaddition. Reaction of **1** and **2b-d** (R=CH$_2$-cyclohexyl, CH$_2$C$_6$H$_4$-4-CF$_3$, CH$_2$CH=CH$_2$) gave the cyclobutane-fused pyrrolidines in 41-51% yields similarly.[7] Reaction of RHNCH$_2$−CH= CH−C$_6$H$_4$−X (X = 4-halogen, 4-OCH$_3$) **2e−h** also gave cyclobutane-fused pyrrolidines **3e−h** in 39−48% yields as the isolable major products.

Table 3-1. Reactions of 1,1-dietyl 2-hydrogene ethenetricarboxylate **1** and *E*-cinnamylamines **2a-h**.

Entry[a]	2	R	X	Product (Yield)
1	**2a**	CH$_2$Ph	H	**3a** (43%)
2	**2b**	CH$_2$-cyclohexyl	H	**3b** (51%)
3	**2c**	CH$_2$C$_6$H$_4$-4-CF$_3$	H	**3c** (41%)
4	**2d**	CH$_2$CH=CH$_2$	H	**3d** (42%)
5	**2e**	CH$_2$Ph	F	**3e** (39%)
6	**2f**	CH$_2$Ph	Cl	**3f** (40%)
7	**2g**	CH$_2$Ph	Br	**3g** (40%)
8	**2h**	CH$_2$Ph	OCH$_3$	**3h** (48%)

[a] Results of entries 2-8 are cited from reference 7

The intermediate amide **A** was not observed under the reaction conditions of amide formation (Scheme 3-1). The amide undergoes the first C−C bond formation to give a zwitter-ionic intermediate **B**, which is stabilized by the phenyl group. The second C−C bond formation proceeds, affording a highly strained cyclobutane-fused bicyclic compound **3**.
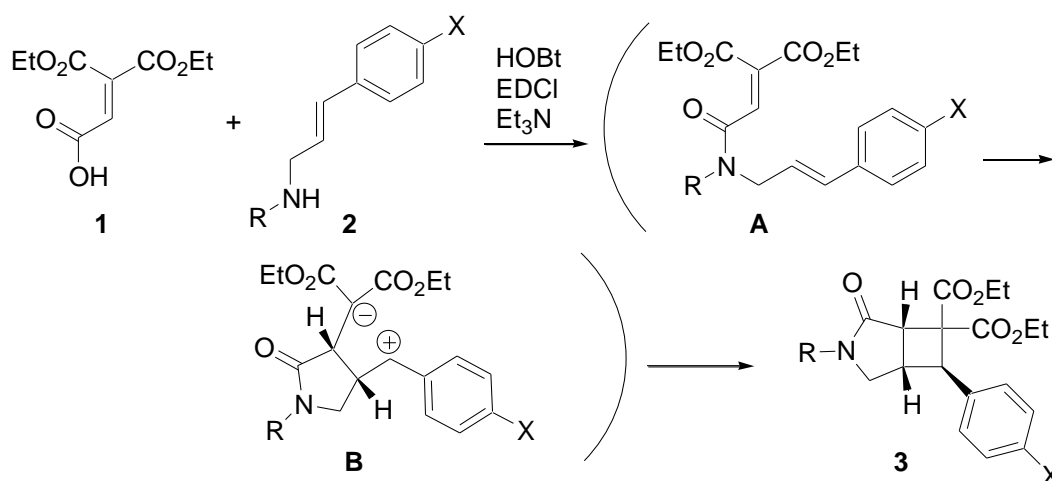
Scheme 3-1. Proposed mechanism for formation of cyclobutane-fused bicyclic compounds **3**.

When the reaction of **1** and **2a** was carried out at 80 °C in 1,2-dichloroethane (ClCH$_2$CH$_2$Cl) or in α,α,α-trifluorotoluene, δ-lactone-fused pyrrolidine **4a** was obtained as the major product in 69% and 50% yields, respectively (Scheme 3-2). The relative configuration of **4** was determined as shown in Scheme 3-2 by NOEs.
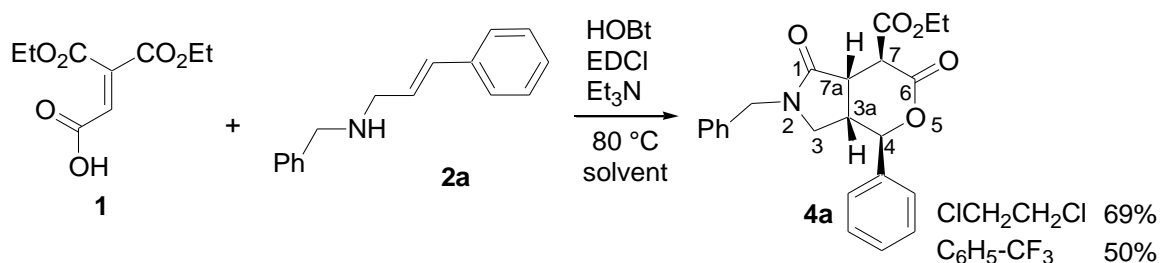
Scheme 3-2. Formation of δ-lactone-fused pyrrolidine **4a**.

Formation of **4** from **3** under the reaction conditions is likely. The reaction conditions may produce a small amount of HCl from EDCI along with formation of the byproducts BtOCH$_2$CH$_2$Cl and BtOCH$_2$CH$_2$OBt.[8] Reaction of cyclobutane products **3** with HCl was next examined. After examining various ring-opening conditions, the reaction of cyclobutane **3a** with 1 equiv of HCl/ether and 1 equiv of H$_2$O in ClCH$_2$CH$_2$Cl at 80 °C for 20 h was found to give **4a** efficiently in 70% yield (Table 3-2, entry 1). The reaction of **3a** with 1 equiv of HCl/H$_2$O in THF at room temperature gave the mixture of alcohol **5a** and **4a** (entry 2). Treatment of alcohol **5a** with 1 equiv of HCl/ether in CH$_2$Cl$_2$ at room temperature overnight gave **4a** quantitatively. On the other hand, in entry 3, the reaction of **3a** with 1 equiv of HCl/ether in CH$_2$Cl$_2$ at room temperature gave Cl-adduct **6a** as a single diastereomer along with **4a**. The stereochemistries of **5a** and **6a** could be deduced as follows.

Table 3-2. Ring-opening reactions of cyclobutane-fused pyrrolidine **3a**.
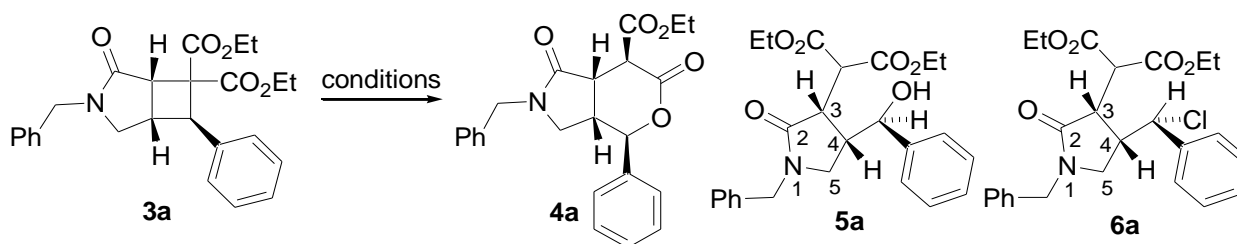
Entry	Conditions	Product (Yield)
1	1 equiv of 1 M HCl/ether, 1 equiv of H$_2$O, ClCH$_2$H$_2$Cl 80 °C	**4a** (70%)
2	1 equiv of 1 M HCl/H$_2$O, THF, r.t.	**5a** (42%), **4a** (47%)
3	1 equiv of 1 M HCl/ether, CH$_2$Cl$_2$, r.t.	**6a** (60%), **4a** (27%)

The 3,4-*cis* stereochemistries of **5a** and **6a** were determined by NOEs. Preferred conformations of **5a** and **6a** may be as depicted in Figure 3-1 from the coupling constants and consideration of steric effects, respectively. The coupling constant between C*H*(OH)Ph and C4−*H* of **5a** (J = 10.9 Hz) and that between C*H*ClPh and C4−*H* of **6a** (J = 4.3Hz) suggest the configurations of the side-chains, as shown in figure 3-1. The similarity in the coupling constant

between C*H*OHPh and C4−*H* of **5a** and that between C4−*H* and C3a−*H* of **4a** (J = 11.3 Hz)

supports the assignment of the configuration of **5a**.
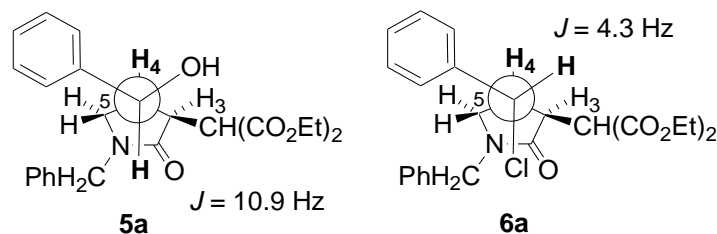
Figure 3-1. Conformations of **5a** and **6a**.

Thus, δ-lactone **4** may form from cyclobutane **3** via intermiediate **B-H$^+$** and alcohol **5**,

followed by transesterification (Scheme 3-3). Formation of **5** may proceed in two steps and

formation of Cl-adducts **6** may proceed in one step ring opening based on their suggested

stereochemistries.
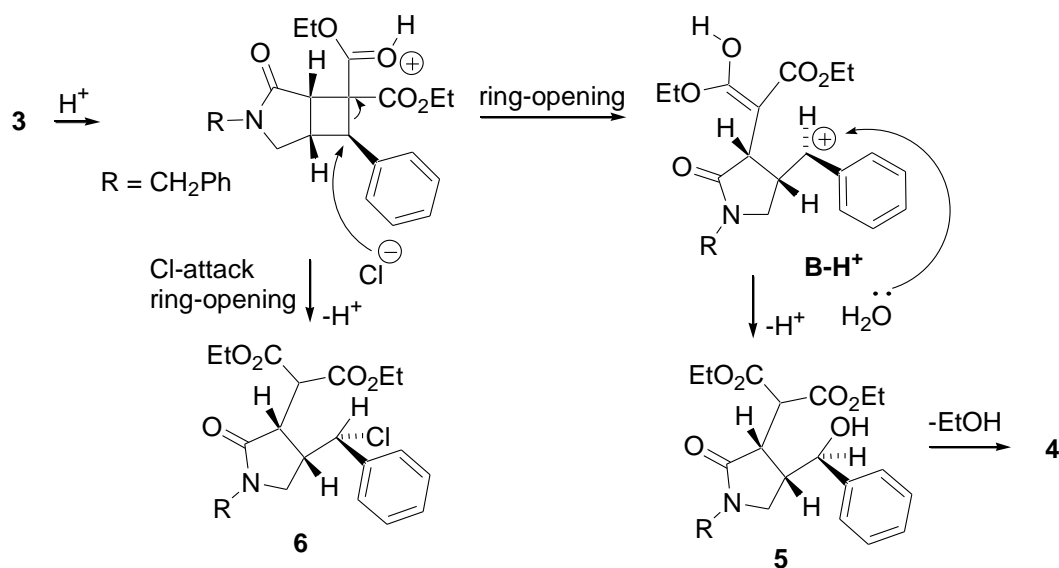
Scheme 3-3. Reaction mechanism of formation of **4**, **5**, and **6**.

Next, the reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and cinnamylamines

bearing electron-withdrawing groups on *ortho* and *para* positions in the presence of the amide

condensation reagents was examined. Interestingly, reaction of **1** and PhCH₂HNCH₂−

CH=CH−C₆H₄−X (X = 2- or 4-NO₂, CN, CO₂Me, CO₂Et, or CF₃) **2i−n** with EDCI/HOBt/Et₃N at

room temperature, 60 °C, and 80 °C gave tetrahydrobenz[*f*]isoindolines **7** as the major products

via [4 + 2] cycloaddition (Table 3-3). The *trans*-fused pyrrolidine stereochemistry of **7** was

determined by NOEs (in C₆D₆, CD₃CN, or (CD₃)₂CO, for some products).

Table 3-3. [4 + 2] Cycloaddition reaction of **1** and electron-withdrawing group substituted
cinnamylamines **2**.
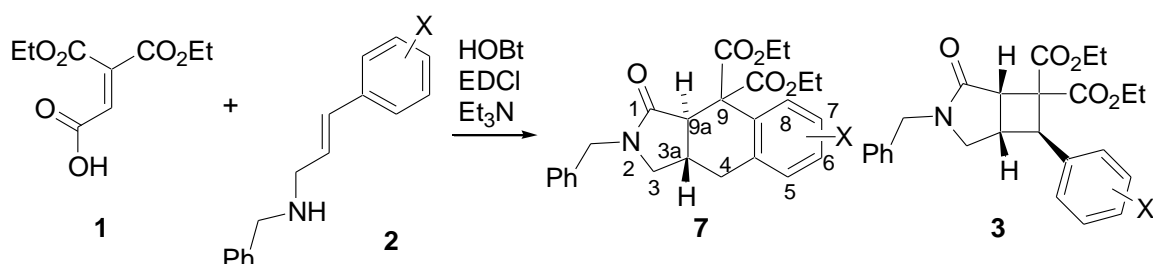
Entry	2	X	Solvent	Temp.	7 Yield(%)	X	3 Yield(%)
1ᵃ	**2i**	2-NO₂	THF	r.t.	75%	5-NO₂	
2ᵃ	**2i**	2-NO₂	Benzene	80 °C	54%	5-NO₂	
3	**2j**	4-NO₂	THF	r.t.	46%	7-NO₂	
4	**2j**	4-NO₂	THF	60 °C	68%	7-NO₂	
5	**2j**	4-NO₂	ClCH₂CH₂Cl	80 °C	66%	7-NO₂	
6	**2k**	4-CN	THF	r.t.	71%	7-CN	
7	**2k**	4-CN	THF	60 °C	75%	7-CN	
8	**2l**	4-CO₂Me	THF	r.t.	71%	7- CO₂Me	ᵇ
9	**2l**	4-CO₂Me	THF	60 °C	66%	7- CO₂Me	ᵇ
10	**2m**	4-CO₂Et	THF	r.t.	57%	7- CO₂Et	ᵇ
11	**2m**	4-CO₂Et	THF	60 °C	56%	7- CO₂Et	ᵇ
12	**2n**	4-CF₃	THF	r.t.	49%	7-CF₃	3%
13	**2n**	4-CF₃	THF	60 °C	48%	7-CF₃	6%
14	**2n**	4-CF₃	Benzene	80 °C	51%	7-CF₃	3%

ᵃ Results of entries 1 and 2 are cited from reference 7. ᵇ A small amount of cyclobutane-
fused pyrrolidine **3** was detected but could not be isolated.

Formation of the zwitter-ionic intermediate **B** corresponding to that in Scheme 3-1 may be strongly destabilized by the resonance and inductive effects of *ortho* and *para* electron-withdrawing group on the benzene ring (Scheme 3-4). Instead, the interaction between a styrene moiety and an alkene moiety of ethenetricarboxylate may lead to the IMDA adduct **C**. The 1,3-H transfer isomerization of **C** to the products **7** may proceed by a stepwise process via intermediate **D-H$^+$**.
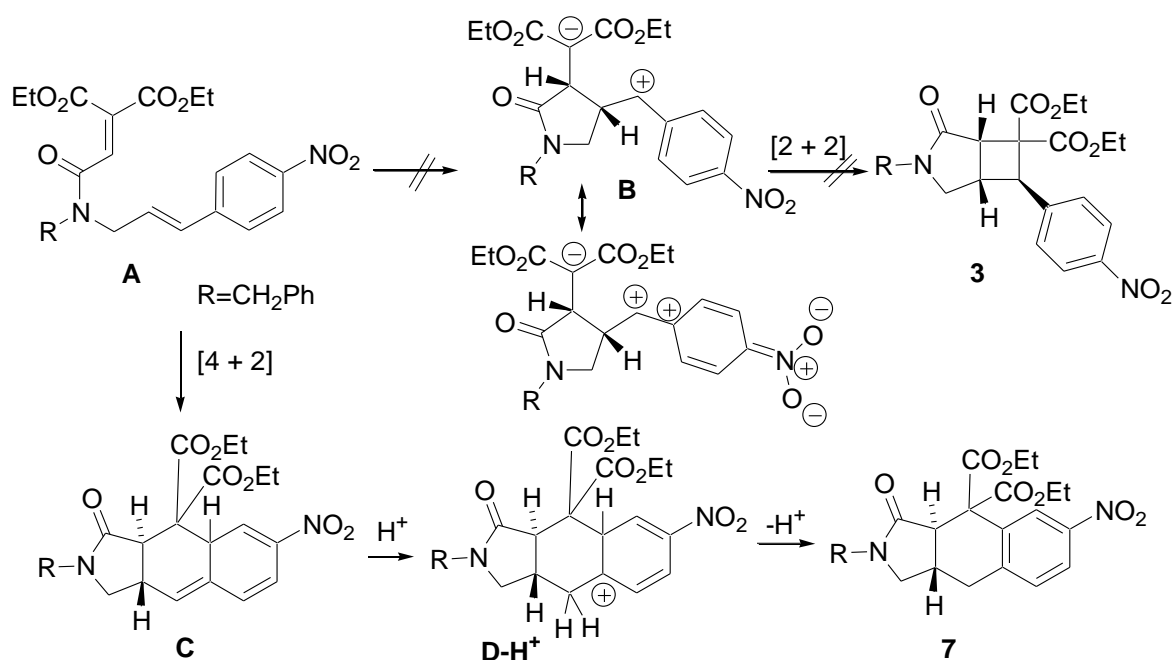
Scheme 3-4. Reaction mechanism of formation **7**.

In order to examine the effects of electron-withdrawing group in [4 + 2] cycloaddition of a styrene moiety and the generality of the reaction, the reactions of other electron-deficient olefins **8-10** with the carboxyl group and cinnamylamines without substituents **2a** and with *o*-NO$_2$ group **2i** were carried out (Table 3-4). Reaction of monomethyl maleate **8** and **2a** or **2i** with EDCI/HOBt/Et$_3$N at room temperature gave amides **11a** and **11i** as isolable products along with the corresponding *trans* isomers **12** (Table 3-4, entries 1, 2). Formation of byproducts **12** may arise from partial isomerization of **8** to **9** under the reaction conditions. Reaction of

monomethyl fumarate **9** and **2a** or **2i** gave amides **12a** and **12i** respectively. Reaction of 4,4,4-trifluoro-3-(trifluoromethyl)-crotonic acid **10** and **2i** with EDCI/HOBt/Et$_3$N at room temperature gave amide **13i** in 57% yield.

Table 3-4. Reactions of electron-deficient olefins **8-10** with carboxyl group and cinnamylamines.
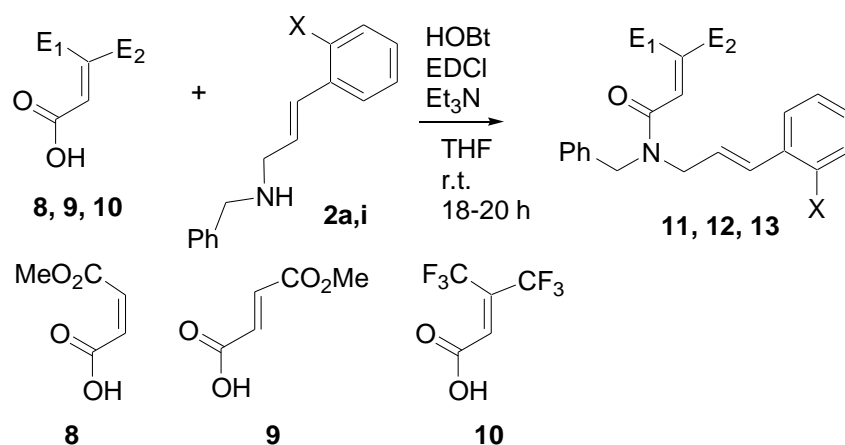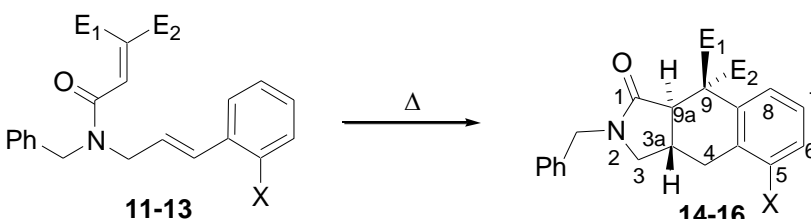
Entry[a]	8-10	E$_1$	E$_2$	2	X	Product	E$_1$	E$_2$	Yield(%)
1	8	CO$_2$Me	H	2a	H	11a [b]	CO$_2$Me	H	40
2	8	CO$_2$Me	H	2i	2-NO$_2$	11i [c]	CO$_2$Me	H	40
3	9	H	CO$_2$Me	2a	H	12a [d]	H	CO$_2$Me	89
4	9	H	CO$_2$Me	2i	2-NO$_2$	12i [b]	H	CO$_2$Me	72
5	10	CF$_3$	CF$_3$	2i	2-NO$_2$	13i	CF$_3$	CF$_3$	57

[a] Results of entries 1-4 are cited from reference 7. [b] A small amount of impurity could not be removed. [c] **12a** could be formed but not confirmed. [d] **12i** was formed in 11% yield as byproduct.

Compound **11i** gradually changes to **14i** at room temperature. Heating **11i** at 80 °C in ClCH$_2$CH$_2$Cl for 18 h gave **14i** via [4 + 2] cycloaddition/H-transfer.[7] On the other hand, heating **11a** at 80 °C in ClCH$_2$CH$_2$Cl for 18 h gave complex mixtures. The reaction of **12i** at 110 °C in toluene for 18 h gave **15i** as isolable products (Table 3-5). Reaction of **12a** at 80 °C in ClCH$_2$CH$_2$Cl for 18 h remained starting materials, and the reaction at 110 °C in toluene for 18 h gave complex mixtures. The stereochemistries of **14i** and **15i** were determined by NOEs. The pyrrolidine ring junction is *trans*. Thermal [4 + 2] cycloaddition reaction of **11i** and **12i** proceeded

stereospecifically, and the product retained the original *cis* and *trans* stereochemistries of C=C double bonds. Thermal reaction of **13i** at 80 °C in ClCH$_2$CH$_2$Cl for 22 h gave ca. 1:1 mixture of **13i** and **16i**. Heating **13i** at 110 °C in toluene for 20 h completed the conversion, and **16i** was obtained in 89% yield.

Table 3-5. Thermal reaction of amide derivatives.

Entry[a]	**11-13**	R$_1$	R$_2$	X	Temp.	Product (Yield)
1	**11a**	CO$_2$Me	H	H	80 °C	**14a** (0)[b]
2	**11i**	CO$_2$Me	H	2-NO$_2$	80° C	**14i** (33)
3	**12a**	H	CO$_2$Me	H	110 °C	**15a** (0)[b]
4	**12i**	H	CO$_2$Me	2-NO$_2$	110 °C	**15i** (31)
5	**13i**	CF$_3$	CF$_3$	2-NO$_2$	110 °C	**16i** (89)

[a] Results of entries 1-4 are cited from reference 7. [b] Complex mixtures.

Higher reactivity of **11** than that of **13** may arise from preferable steric overlap on the transition states of [4 + 2] cycloaddition (Scheme 3-5). Much higher reactivity of ethenetricarboxylate intermediates **A** compared to **11** and **13** may arise from activation of C=C double bond by three electron-withdrawing carbonyl groups. Lower reactivity of **13** than that of **A** could be due to the steric effect of CF$_3$ groups.

Scheme 3-5. Steric efficients in [4 + 2] cycloaddition.

3-3 Conclusion

In summary, intramolecular [2 + 2] and [4 + 2] (IMDA) cycloaddition reactions of cinnamylamides and ethenetricarboxylate in sequential processes have been studied. Reaction of cinnamylamines without substituents on the benzene ring and with halogens and OMe on *para* positions at room temperature gave cyclobutane-fused pyrrolidines as the major products via [2 + 2] cycloaddition. The reaction at 80 °C in 1.2-dichloroethane gave δ-lactone-fused pyrrolidines as the major products, possibly via ring-opening of the cyclobutanes. Interestingly, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and cinnamylamines bearing electronwithdrawing groups such as NO_2, CN, CO_2Me, CO_2Et, or CF_3 on *ortho* and *para* positions in the presence of EDCI/HOBt/ Et_3N at room temperature or at 60−80 °C gave tetrahydrobenz[*f*]isoindolines via IMDA reaction as the major products. Diversity of the reaction pattern depending on the substituents of the benzene ring was found. The synthesized highly functionalized heterocyclic products and promising as useful precursors to synthesize functionalmaterials and physiologically active substances.

3-4 Experimental Section

General Procedures

[1]H Chemical shifts are reported in ppm relative to Me$_4$Si. [13]C Chemical shifts are reported in ppm relative to CDCl$_3$ (77.1 ppm). [19]F Chemical shifts are reported in ppm relative to CFCl$_3$. [13]C Mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI, FAB, or ESI. Mass analyzer type used for EI, FAB, and is double-focusing and that for ESI is TOF in the HRMS measurements. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75−150 μm).

Ethenetricarboxylate **1** was prepared according to the literature.[9] Cinnamylamines **2a−n** were prepared from the corresponding cinnamaldehydes and amines by reductive amination in methanol (for **2a−l**, **2n**) or ethanol (for **2m**) according to the literature procedure.[10] ^{1}H NMR of **2a** was in accord with the reported data.[11]

4-cyanocinnamaldehyde (86%) was prepared from the corresponding benzaldehydes and acetoaldehyde according to the literature procedure.[12] ^{1}H NMR spectra of 4-cyanocinnamaldehydewas in accord with the reported data. [13] 4-(Methoxycarbonyl)cinnamaldehyde (59%) was prepared by the palladium-catalyzed reaction of the corresponding aryl iodides with acrolein diethyl acetal.[13] ^{1}H NMR spectra of 4-(methoxycarbonyl)cinnamaldehyde were in accord with the reported data. [14] 4-(Ethoxycarbonyl)cinnamaldehyde was prepared according to the literature.[13] 4-(Trifluoromethyl)-cinnamaldehyde (58%) was prepared from the corresponding benzaldehydes and formylmethylenetriphenylphosphorane according to the literature procedure.[15]

4-(Trifluoromethyl)cinnamaldehyde: (8.2 mmol scale, 0.951 g, 58%); R$_f$ = 0.6 (hexane−ether = 1:1); pale yellow crystals; mp 60 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.78 (dd, J = 16.0, 7.6 Hz, 1H), 7.52 (d, J = 16.0 Hz, 1H), 7.69 (s, 4H), 9.76 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 123.7 (C, q, J_{CF} = 272 Hz), 126.0 (CH, q, J_{CF} = 3.8 Hz), 128.6 (CH), 130.5 (CH), 132.4 (C, q, J_{CF} = 33 Hz), 137.3 (C, q, J_{CF} = 1.5 Hz), 150.3 (CH), 193.2 (CH); ^{19}F NMR (376 MHz, CDCl$_3$) δ

(ppm) -63.05; IR (KBr) 2817, 2733, 1680, 1324, 1172, 1122, 1066 cm^{-1}; MS (EI) *m/z* 200 (M$^+$, 38), 199 (32), 151 (47), 131 (100%); HRMS (EI) *m/z* M$^+$ 200.0448 (calcd for C$_{10}$H$_7$F$_3$O 200.0449).

Typical experimental procedure for preparation of cinnamylamines 2. A solution of 4-nitrocinnamaldehyde (1.771 g, 10 mmol) and benzylamine (0.954 g, 8.9 mmol) in methanol (6.8 mL) was heated under reflux for 30 min, followed by the portionwise addition of NaBH$_4$ (567 mg, 15 mmol) in ice-cooled bath. The mixture was stirred overnight at room temperature. Excess sodium borohydride was quenched by the addition of acetone (3.7 mL). The mixture was concentrated, and the residue was dissloved in CH$_2$Cl$_2$ and water. The organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography over silica gel eluting with hexane−Et$_2$O to give **2j** (1.08 g, 45%).

Benzyl 4-nitrocinnamylamine (2j): (8.9 mmol scale, 1.08 g, 45%); R$_f$ = 0.2 (hexane−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.68 (bs, 1H), 3.49 (dd, *J* = 5.9, 1.4 Hz, 2H), 3.85 (s, 2H), 6.50 (dt, *J* = 16.0, 5.9 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 7.24−7.30 (m, 1H), 7.31−7.35 (m, 4H), 7.47 (d-like, *J* = 8.9 Hz, 2H), 8.15 (d-like, *J* = 8.9 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.9 (CH$_2$), 53.5 (CH$_2$), 124.0 (CH), 126.7 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 129.1 (CH), 133.8 (CH), 134.0 (C), 143.7 (C), 146.8 (C); IR (neat) 3328, 3027, 2833, 1651, 1595, 1520, 1494, 1454, 1346, 1110, 971 cm^{-1}; MS (EI) *m/z* 268 (M$^+$, 6.9), 196 (16), 132 (23), 91 (100%); HRMS (EI) *m/z* M$^+$ 268.1207 (calcd for C$_{16}$H$_{16}$N$_2$O$_2$ 268.1212).

Benzyl 4-cyanocinnamylamine (2k): (6.4 mmol scale, 0.837 g, 53%); R$_f$ = 0.2 (hexane−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.55 (bs, 1H), 3.47 (dd, *J* = 5.9, 1.4 Hz, 2H), 3.84 (s, 2H), 6.44 (dt, *J* = 15.9, 5.9 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 7.24− 7.30 (m, 1H), 7.32−7.35 (m, 4H), 7.42 (d-like, *J* = 8.4 Hz, 2H), 7.57 (d-like, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.9 (CH$_2$), 53.5 (CH$_2$), 110.5 (C), 119.0 (C), 126.7 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 129.5 (CH), 132.4 (CH), 132.8 (CH), 140.0 (C), 141.7 (C); IR (neat) 3315, 3028, 2821, 2224, 1651,

1604, 1495, 1453, 1412, 1360, 1175, 1118, 971 cm^{-1}; MS (EI) m/z 248 (M$^+$, 13), 196 (10), 146 (32), 106 (34), 91 (100%); HRMS(EI) m/z M$^+$ 248.1317 (calcd for C$_{17}$H$_{16}$N$_2$ 248.1313).

Benzyl 4-(methoxycarbonyl)cinnamylamine (2l): (5 mmol scale, 0.625 g, 44%); R$_f$ = 0.2 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.52 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.85 (s, 2H), 3.90 (s, 3H), 6.44 (dt, J = 15.9, 6.1 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 7.22−7.29 (m, 1H), 7.31−7.35 (m, 4H), 7.41 (d, J = 8.3 Hz, 2H), 7.97 (d-like, J = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 51.1 (CH$_2$), 52.1 (CH$_3$), 53.5 (CH$_2$), 126.2 (CH), 127.1 (CH), 128.2 (CH), 128.5 (CH), 128.8 (C), 130.0 (CH), 130.4 (CH), 131.5 (CH), 140.2 (C), 141.7 (C), 167.0 (C); IR (neat) 3326, 3028, 2950, 1721, 1606, 1454, 1435, 1281, 1178, 1109, 1017, 971 cm^{-1}; MS (EI) m/z 281 (M$^+$, 14), 132 (35), 106 (25), 91 (100%); HRMS (EI) m/z M$^+$ 281.1417 (calcd for C$_{18}$H$_{19}$NO$_2$ 281.1416).

Benzyl 4-(ethoxycarbonyl)cinnamylamine (2m): (6 mmol scale, 0.832 g, 47%); R$_f$ = 0.2 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.39 (t, J = 7.1 Hz, 3H), 1.56 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.85 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.43 (dt, J = 15.9, 6.1 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 7.24−7.29 (m, 1H), 7.31−7.36 (m, 4H), 7.41 (d-like, J = 8.4 Hz, 2H), 7.98 (d-like, J = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.4 (CH$_3$), 51.2 (CH$_2$), 53.5 (CH$_2$), 60.9 (CH$_2$), 126.1 (CH), 127.1 (CH), 128.2 (CH), 128.5 (CH), 129.2 (C), 129.9 (CH), 130.4 (CH), 131.3 (CH), 140.2 (C), 141.6 (C), 166.5 (C); IR (neat) 3316, 2980, 1713, 1607, 1495, 1453, 1413, 1366, 1275, 1178, 1105, 1020, 972 cm^{-1}; MS (EI) m/z 295 (M$^+$, 31), 204 (20), 132 (71), 91 (100%); HRMS (EI) m/z M$^+$ 295.1581 (calcd for C$_{19}$H$_{21}$NO$_2$ 295.1572).

Benzyl 4-(trifluoromethyl)cinnamylamine (2n): (3.6 mmol scale, 0.996 g, 96%); R$_f$ = 0.5 (hexane−ether = 1:1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.55 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.84 (s, 2H), 6.41 (dt, J = 15.8, 6.1 Hz, 1H), 6.58 (d, J = 15.8 Hz, 1H), 7.25−7.30 (m, 1H), 7.32−7.35 (m, 4H), 7.44 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 51.1 (CH$_2$), 53.5 (CH$_2$), 124.1 (C, q, J_{CF} = 272 Hz), 125.6

(CH, q, J_{CF} = 3.8 Hz), 126.5 (CH), 127.2 (CH), 128.3 (CH), 128.6 (CH), 129.2 (C, q, J = 32 Hz), 130.0 (CH), 131.4 (CH), 140.2 (C), 140.7 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −62.50; IR (neat) 3310, 3029, 2823, 1652, 1615, 1495, 1455, 1415, 1327, 1163, 1120, 1067, 1016, 970 cm^{-1};MS (EI) m/z 291 (M$^+$, 100), 200 (11), 185 (35), 132 (67), 91 (100%); HRMS (EI) m/z M$^+$ 291.1235 (calcd for C$_{17}$H$_{16}$F$_3$N 291.1235).

Typical experimental procedure for preparation of 3, 7, 11-13 (Table 3-1, entry 1). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF$_3$CO$_2$H (4 mL))[9] in THF (0.7 mL) were added benzyl cinnamylamine (**2a**) (223 mg, 1 mmol) in THF (0.7 mL), Et$_3$N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol), and EDCI (1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **3a** (180 mg, 43%).

3a: R$_f$ = 0.1 (hexane-ether = 1 : 8); colorless crystals; mp 137− 138.5 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.29 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.39 (ddd, J = 10.7, 7.0, 5.9 Hz, 1H), 2.67 (d, J =10.7 Hz, 1H), 3.31 (dd, J = 10.7, 5.9 Hz, 1H), 3.89 (d, J = 7.0 Hz, 1H), 3.89 (d, J = 14.3 Hz, 1H), 4.03-4.17 (m, 2H), 4.22-4.36 (m, 3H), 4.89 (d, J = 14.3 Hz,1H), 6.75 (d-like, J = 7.6 Hz, 2H), 7.22-7.42 (m, 8H). Selected NOEs are between δ 2.39 (C5-*H*) and δ 3.31 (C4-H*H*), 6.75 (Ar-*H*), 3.89 (C1-*H*). Atom numbering is shown in Table 3-1.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.5 (CH$_3$), 15.0 (CH$_3$), 36.1 (CH), 41.1 (CH), 44.8 (CH$_2$), 46.4 (CH$_2$), 59.9 (CH$_2$), 64.8 (CH$_2$), 79.2 (C), 79.8 (CH), 127.4 (CH), 127.9 (CH), 128.7 (CH), 128.9 (CH), 129.05

(CH), 129.11 (CH), 136.6 (C), 136.8 (C), 163.0 (C), 167.3 (C), 173.1 (C). Selected HMBC correlations are between δ 2.39 (C5-H), 2.67 (C4-HH), 3.89 (C1-H) and δ 173.1 (C2), between δ 2.39 (C5-H), 2.67 (C4-HH), 3.31 (C4-HH), 3.89 (C1-H) and δ 79.8 (C6), between δ 2.67 (C4-HH) and δ 41.1 (C1) and between δ 2.67 (C4-HH), 3.31 (C4- HH), 3.89 (C1-H) and δ 36.1 (C5).; IR (KBr) 2981, 1699, 1634, 1285, 1079 cm^{-1}; MS (EI) m/z 421 (M$^+$, 14), 222 (42), 199 (58), 132 (63), 91 (100%); HRMS m/z M$^+$ 421.1886 (calcd for $C_{25}H_{27}NO_5$ 421.1889).

Typical experimental procedure for preparation of 4a. To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-tert-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF_3CO_2H (4 mL))[9] in 1,2-dichloroethane (0.7 mL) were added benzyl cinnamylamine (**2a**) (201 mg, 0.90 mmol) in 1,2-dichloroethane (0.7 mL), Et$_3$N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol), and EDCI (1-[3-(dimethylamino)propyl]- 3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to 80 °C and then stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$, and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane−Et$_2$O to give **4a** (246 mg, 69%).

4a: R$_f$ = 0.1 (hexane−ether = 1:4); colorless crystals; mp 107.5− 108 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.39 (t, J = 7.1 Hz, 3H), 2.78−2.86 (m, 2H), 3.28 (dd, J = 11.2, 7.9 Hz, 1H), 3.26−3.78 (m, 2H), 4.33 (d, J = 14.4 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.55 (d, J = 14.4 Hz, 1H), 4.78 (d, J = 11.3 Hz, 1H), 7.07 (d-like, J = 8.0 Hz, 2H), 7.21−7.24 (m, 2H), 7.29−7.39 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.2 (CH$_3$), 37.2 (CH), 41.1 (CH), 45.9 (CH$_2$), 46.8 (CH$_2$), 47.1 (CH), 62.5 (CH$_2$), 81.4 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.7 (CH), 135.2 (C), 135.7 (C), 167.5 (C), 167.6 (C), 172.2 (C); ^{1}H NMR (400 MHz, CD$_3$CN) δ

(ppm) 1.33 (t, J = 7.1 Hz, 3H), 2.70 (dd, J = 10.8, 1.9 Hz, 1H), 3.00 (dddd, J = 11.7, 10.1, 8.2, 1.9 Hz, 1H), 3.26 (dd, J = 10.8, 8.2 Hz, 1H), 3.65 (dd, J = 10.6, 10.1 Hz, 1H), 3.83 (d, J = 10.6 Hz, 1H), 4.30 (d, J = 14.8 Hz, 1H), 4.317 (q, J = 7.1 Hz, 1H), 4.320 (q, J = 7.1 Hz, 1H), 4.48 (d, J = 14.8 Hz, 1H), 5.10 (d, J = 11.7 Hz, 1H), 7.22−7.26 (m, 4H), 7.30−7.40 (m, 6H). Selected NOEs are between δ 3.00 (C3a−H) and δ 3.26 (C3−HH), 3.65 (C7a−H) and between δ 2.70 (C3−HH) and δ 5.10 (C4−H). Atom numbering is shown in Scheme 3-2. ^{13}C NMR (100.6 MHz, CD$_3$CN) δ (ppm) 14.5 (CH$_3$), 36.8 (CH), 41.9 (CH), 46.8 (CH$_2$), 46.9 (CH$_2$), 48.2 (CH), 62.7 (CH$_2$), 82.1 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 130.4 (CH), 137.0 (C), 137.4 (C), 169.0 (C), 169.3 (C), 173.2 (C). Selected HMBC correlations are between δ 2.70 (C3−HH), 3.26 (C3−HH), 3.00 (C3a−H), 3.65 (C7a−H) and δ 82.1 (C4), between δ 3.65 (C7a−H) and δ 48.2 (C7), and between δ 2.70 (C3−HH), 5.10 (C4−H) and δ 41.9 (C7a). IR (KBr) 3448, 2929, 1752, 1740, 1691, 1449, 1375, 1266, 1156, 1045, 1021 cm^{-1}; MS (EI) m/z 393 (M$^+$, 16), 186 (30), 91 (61), 57 (100%); HRMS (EI) m/z M$^+$ 393.1574 (calcd for C$_{23}$H$_{23}$NO$_5$ 393.1576).

Transformation of 3a to 4a (Table 3-3, entry 1). To a solution of **3a** (210 mg, 0.5 mmol) in ClCH$_2$CH$_2$Cl (0.7 mL) were added 1 M HCl/ether (0.5 mL, 0.5 mmol) and H$_2$O (9 mg, 0.5 mmol). The mixture was stirred at 80 °C for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane−Et$_2$O to give **4a** (139 mg, 70%). Transformation of 3a to **5a** and **4a** (Table 3-2, entry 2). To a solution of **3a** (245 mg, 0.58 mmol) in THF (0.8 mL) was added 1 M HCl/H$_2$O (0.58 mL, 0.58 mmol). The mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH$_2$Cl$_2$. The organic phase was washed with water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane−Et$_2$O to give **5a** (111 mg, 42%) and **4a** (107 mg, 47%).

5a: Rf = 0.6 (ether); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.15 (bs, 1H), 2.54 (dd, J = 10.3, 2.6 Hz, 1H), 2.87 (dddd, J = 10.9, 7.4, 6.6, 2.6 Hz, 1H), 2.97 (dd, J = 10.2, 6.6 Hz, 1H), 3.67 (dd, J = 10.2, 7.4 Hz, 1H), 4.06 (d, J = 14.5 Hz, 1H), 4.08 (d, J = 10.2 Hz, 1H), 4.19−4.39 (m, 5H), 4.58 (d, J = 14.5 Hz, 1H), 6.87−6.89 (m, 2H), 7.16−7.23 (m, 5H), 7.29−7.35 (m, 3H). Selected NOEs are between δ 3.67 (C3−H) and δ 2.87 (C4−H), 2.97 (C5−HH) and between δ 2.54 (C5−HH), 2.97 (C5− HH), and δ 6.87−6.89 (Ph−H). Atom numbering is shown in Table 3-2. ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.2 (CH$_3$), 42.2 (CH), 46.0 (CH), 46.6 (CH$_2$), 47.5 (CH$_2$), 51.1 (CH), 61.6 (CH$_2$), 61.8 (CH$_2$), 4.0 (CH), 126.7 (CH), 127.8 (CH), 128.4 (CH), 128.69 (CH), 128.76 (CH), 128.77 (CH), 136.4 (C), 142.5 (C), 168.6 (C), 169.4 (C), 172.8 (C). Selected HMBC correlations are between δ 2.54 (C5−HH), 2.87 (C4−H), 3.67 (C3−H), and δ 172.8 (*C*2), between δ 2.54 (C5−HH), 2.87 (C4−H), 2.97 (C5−HH), and δ 74.0 (*C*H(OH)Ph), and between δ 2.54 (C5−HH), 2.97 (C5−HH), 3.67 (C3−H), and δ 42.2 (*C*4). IR (neat) 3419, 2981, 1747, 1732, 1684, 1494, 1455, 1376, 1301, 1032 cm^{-1}; MS (EI) *m/z* 439 (M$^+$, 15), 393 (13), 332 (33), 174 (70), 84 (100%); HRMS (EI) *m/z* M$^+$ 439.2003 (calcd for C$_{25}$H$_{29}$NO$_6$ 439.1995).

Transformation of 3a to 6a (Table 3-2, entry 3). To a solution of **3a** (178 mg, 0.42 mmol) in CH$_2$Cl$_2$ (0.6 mL) was added 1 M HCl/ ether (0.42 mL, 0.42 mmol). The mixture was stirred at room temperature or 20 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane−Et$_2$O to give **6a** (117 mg, 60%) and **4a** (45 mg, 27%).

6a: R$_f$ = 0.7 (hexane−ether = 1:8); pale yellow oil; ^{1}H NMR (400MHz, CDCl$_3$) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 3.19 (dd, J = 10.4, 2.7 Hz, 1H), 3.24 (dd, J = 10.4, 7.1 Hz, 1H), 3.32 (dddd, J = 8.7, 7.1, 4.3, 2.7 Hz, 1H), 3.62 (dd, J = 10.5, 8.7 Hz, 1H), 3.85 (d, J = 10.5 Hz, 1H), 4.15−4.41 (m, 5H), 4.67 (d, J = 14.7 Hz, 1H), 4.95 (d, J = 4.3 Hz, 1H), 7.26−7.36 (m,

10H). Selected NOEs are between δ 3.62 (C3$-$*H*) and δ 3.32 (C4$-$*H*), 3.24 (C5$-$H*H*) and between δ 3.85 (C*H*(CO$_2$Et)$_2$), 3.19 (C5$-$*H*H), and δ 4.95 (C*H*ClPh). Atom numbering is shown in Table 3-2. ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.1 (CH$_3$), 14.2 (CH$_3$), 41.4 (CH), 44.7 (CH), 46.6 (CH$_2$), 46.9 (CH$_2$), 49.8 (CH), 61.95 (CH), 61.98 (CH$_2$), 62.2 (CH$_2$), 127.0 (CH), 127.8 (CH), 128.5 (CH), 128.66 (CH), 128.72 (CH), 128.8 (CH), 135.8 (C), 138.9 (C), 168.4 (C), 168.5 (C), 171.9 (C). Selected HMBC correlations are between δ 3.19 (C5$-$*H*H), 3.24 (C5$-$H*H*), 3.62 (C3$-$*H*), and δ 171.9 (*C*2), between δ 3.19 (C5$-$*H*H), 3.24 (C5$-$H*H*), 3.62 (C3$-$*H*), and δ 61.95 (*C*HClPh), and between δ 3.19 (C5$-$*H*H), 3.24 (C5$-$H*H*), and δ 41.4 (*C*4). IR (neat) 2981, 1747, 1732, 1689, 1604, 1495, 1447, 1371, 1028 cm^{-1}; MS (EI) *m/z* 459 (M$^+$, 6.3), 457 (M$^+$, 17), 332 (33), 198 (52), 72 (100%); HRMS (EI) *m/z* M$^+$ 457.1655, 459.1647 (calcd for C$_{25}$H$_{28}$ClNO$_5$ 457.1656, 459.1627).

7j: (1 mmol scale, 317 mg, 68%); R$_f$ = 0.3 (hexane$-$ether = 1:8); colorless crystals; mp 133$-$134.5 °C (AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.25 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 2.55 (ddddd, *J* = 12.9, 12.1, 9.6, 7.5, 5.1 Hz, 1H), 2.90 (dd, *J* = 17.0, 12.1 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 3.07 (dd, *J* = 9.6, 9.3 Hz, 1H), 3.14 (dd, *J* = 17.0, 5.1 Hz, 1H), 3.48 (dd, *J* = 9.3, 7.5 Hz, 1H), 4.15 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.28$-$4.51 (m, 4H), 4.68 (d, *J* = 14.8 Hz, 1H), 7.27$-$7.37 (m, 6H), 8.08 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.30 (d, *J* = 2.3 Hz, 1H); Atom numbering is shown in Table 3-3. ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 32.3 (CH), 34.4 (CH$_2$), 46.6 (CH$_2$), 50.1 (CH), 50.2 (CH$_2$), 60.4 (C), 62.5 (CH$_2$), 63.2 (CH$_2$), 122.8 (CH), 126.2 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 130.7 (CH), 135.9 (C), 136.6 (C), 143.1 (C), 146.6 (C), 167.6 (C), 169.9 (C), 171.0 (C); ^{1}H NMR (400 MHz, (CD$_3$)$_2$CO) δ (ppm) 1.19 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.54 (ddddd, *J* = 12.9, 11.9, 9.6, 7.6, 5.3 Hz, 1H), 3.06 (dd, *J* = 17.8, 11.9 Hz, 1H), 3.11 (d, *J* = 12.9 Hz, 1H), 3.22 (dd, *J* = 9.6, 9.0 Hz, 1H), 3.26 (dd, *J* = 17.8, 5.3 Hz, 1H), 3.54 (dd, *J* = 9.0, 7.6 Hz, 1H), 4.08$-$4.42 (m, 5H), 4.69 (d, *J* = 15.0 Hz, 1H), 7.27$-$7.32 (m, 1H), 7.33$-$7.37 (m, 4H), 7.50 (d, *J* = 8.6 Hz, 1H), 8.11 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.23 (d, *J* = 2.3 Hz, 1H). Selected NOEs are between δ 2.54

(C3a−H) and δ 3.54 (C3−H*H*), 3.26 (C4−H*H*). ^{13}C NMR (100.6 MHz, (CD$_3$)$_2$CO) δ (ppm) 14.1 (CH$_3$), 14.3 (CH$_3$), 33.1 (CH), 34.7 (CH$_2$), 46.6 (CH$_2$), 50.3 (CH), 50.6 (CH$_2$), 61.4 (C), 62.6 (CH$_2$), 63.0 (CH$_2$), 123.2 (CH), 126.2 (CH), 128.1 (CH), 128.7 (CH), 129.3 (CH), 132.0 (CH), 137.0 (C), 138.4 (C), 145.3 (C), 147.1 (C), 168.2 (C), 170.4 (C), 171.3 (C). Selected HMBC correlations are between δ 3.06 (C4−*H*H), 3.11 (C9a−*H*), and δ 50.6 (*C*3), between δ 3.22 (C3−*H*H), 3.54 (C3−H*H*), and δ 50.3 (*C*9a), between δ 3.06 (C4−*H*H), 3.26 (C4−H*H*), 3.11 (C9a−*H*), 3.54 (C3−H*H*), and δ 33.1 (*C*3a), and between δ 3.11 (C9a−*H*) and δ 61.4 (*C*9). IR (KBr) 2982, 2936, 1747, 1732, 1699, 1520, 1347, 1255, 1190, 1098, 1029 cm^{-1}; MS (EI) *m/z* 466 (M$^+$, 96), 363 (53), 91 (100%); HRMS (EI) *m/z* M$^+$ 466.1734 (calcd for C$_{25}$H$_{26}$N$_2$O$_7$ 466.1740). Anal. Calcd for C$_{25}$H$_{26}$N$_2$O$_7$: C, 64.37; H, 5.62; N, 6.01. Found: C, 64.68; H, 5.34; N, 5.97.

7k: (1 mmol scale, 334 mg, 75%); R$_f$ = 0.2 (hexane−ether = 1:4); colorless crystals; mp 118.5−119.5 °C (AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.25 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 2.52 (ddddd, *J* = 13.3, 12.1, 9.7, 7.4, 5.3 Hz, 1H), 2.87 (dd, *J* = 16.6, 12.1 Hz, 1H), 3.01 (d, *J* = 13.3 Hz, 1H), 3.05 (dd, *J* = 9.7, 9.4 Hz, 1H), 3.08 (dd, *J* = 16.6, 5.3 Hz, 1H), 3.47 (dd, *J* = 9.4, 7.4 Hz, 1H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.28−4.49 (m, 4H), 4.67 (d, *J* = 14.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.27−7.37 (m, 5H), 7.50 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.0 (CH$_3$), 14.1 (CH$_3$), 32.2 (CH), 34.5 (CH$_2$), 46.5 (CH$_2$), 50.1 (CH), 50.2 (CH$_2$), 60.3 (C), 62.5 (CH$_2$), 63.1 (CH$_2$), 110.7 (C), 118.6 (C), 127.7 (CH), 128.2 (CH), 128.8 (CH), 130.8 (CH), 131.1 (CH), 134.9 (CH), 135.7 (C), 136.6 (C), 141.3 (C), 167.6 (C), 170.0 (C), 171.2 (C); ^{1}H NMR (400 MHz, CD$_3$CN) δ (ppm) 1.17 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.44 (ddddd, *J* = 12.9, 11.9, 9.4, 7.6, 5.3 Hz, 1H), 2.91 (dd, *J* = 17.2, 11.9 Hz, 1H), 3.02 (d, *J* = 12.9 Hz, 1H), 3.11 (dd, *J* = 9.4, 9.2 Hz, 1H), 3.11 (dd, *J* = 17.2, 5.3 Hz, 1H), 3.46 (dd, *J* = 9.2, 7.6 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.19−4.38 (m, 4H), 4.62 (d, *J* = 15.2 Hz, 1H), 7.28−7.39 (m, 6H), 7.60 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H). Selected NOEs are between δ 2.44 (C3a−*H*) and δ 3.46 (C3−H*H*), and between δ 2.91 (C4−*H*H) and δ 3.02

(C9a−*H*). ^{13}C NMR (100.6 MHz, CD$_3$CN) δ (ppm) 14.2 (CH$_3$), 14.3 (CH$_3$), 32.9 (CH), 34.7 (CH$_2$), 46.7 (CH$_2$), 50.4 (CH), 51.0 (CH$_2$), 61.4 (C), 62.9 (CH$_2$), 63.4 (CH$_2$), 110.8 (C), 119.3 (C), 128.3 (CH), 128.8 (CH), 129.5 (CH), 132.0 (CH), 132.1 (CH), 135.3 (CH), 136.7 (C), 138.4 (C), 143.3 (C), 168.6 (C), 170.9 (C), 171.9 (C). Selected HMBC correlations are between δ 2.91 (C4−*H*H) and δ 51.0 (*C*3), between δ 3.46 (C3−H*H*) and δ 50.4 (*C*9a), δ 2.91 (C4−*H*H), 3.02 (C9a−H), 3.46 (C3−H*H*), and δ 32.9 (*C*3a), and between δ 3.02 (C9a−H) and δ 61.4 (*C*9). IR (KBr) 2981, 2937, 2229, 1742, 1730, 1696, 1496, 1442, 1366, 1252, 1190, 1029 cm^{-1}; MS (EI) *m/z* 446 (M$^+$, 100), 343 (58), 149 (60), 91 (92%); HRMS (EI) *m/z* M$^+$ 446.1846 (calcd for C$_{26}$H$_{26}$N$_2$O$_5$ 446.1842). Anal. Calcd for C$_{26}$H$_{26}$N$_2$O$_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.59; H, 5.96; N, 6.15.

7l: (1 mmol scale, 342 mg, 71%); R$_f$ = 0.3 (hexane−ether = 1:4); colorless crystals; mp 145−146 °C (AcOEt); ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 1.23 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.53 (ddddd, *J* = 13.2, 12.1, 9.6, 7.4, 5.1 Hz, 1H), 2.86 (dd, *J* = 16.6, 12.1 Hz, 1H), 3.04 (d, *J* = 13.2 Hz, 1H), 3.05 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.08 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.46 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.90 (s, 3H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.26−4.50 (m, 4H), 4.68 (d, *J* = 14.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.26−7.36 (m, 5H), 7.89 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 32.4 (CH), 34.4 (CH$_2$), 46.5 (CH$_2$), 50.28 (CH), 50.32 (CH$_2$), 52.2 (CH$_3$), 60.4 (C), 62.2 (CH$_2$), 62.7 (CH$_2$), 127.6 (CH), 128.2 (CH), 128.6 (C), 128.7 (CH), 128.9 (CH), 129.9 (CH), 132.2 (CH), 134.5 (C), 136.7 (C), 140.8 (C), 166.6 (C), 168.2 (C), 170.4 (C), 171.5 (C); ^{1}H NMR (400 MHz,CD$_3$CN) δ (ppm) 1.16 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.44 (ddddd, *J* = 13.1, 11.9, 9.8, 7.6, 5.3 Hz, 1H), 2.89 (dd, *J* = 17.0, 11.9 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 3.11 (dd, *J* = 17.0, 5.3 Hz, 1H), 3.11 (dd, *J* = 9.8, 9.2 Hz, 1H), 3.47 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.87 (s, 3H), 4.07 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.17−4.38 (m, 5H), 4.62 (d, *J* = 15.0 Hz, 1H), 7.28−7.33 (m, 4H), 7.36−7.39 (m, 2H), 7.86 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.94 (d, *J* = 1.8 Hz, 1H). Selected NOEs are between δ 2.44 (C3a−*H*) and δ 3.47 (C3−H*H*). ^{13}C NMR (100.6 MHz, CD$_3$CN) δ (ppm) 14.2 (CH$_3$), 14.4 (CH$_3$), 33.1 (CH),

34.6 (CH$_2$), 46.7 (CH$_2$), 50.6 (CH), 51.1 (CH$_2$), 52.8 (CH$_3$), 61.6 (C), 62.8 (CH$_2$), 63.1 (CH$_2$), 128.3 (CH), 128.8 (CH), 129.2 (C), 129.4 (CH), 129.6 (CH), 131.3 (CH), 132.4 (CH), 135.8 (C), 138.4 (C), 142.8 (C), 167.2 (C), 169.1 (C), 171.3 (C), 172.1 (C). Selected HMBC correlations are between δ 2.89 (C4−*H*H) and δ 51.1 (*C*3), between δ 3.47 (C3−H*H*) and δ 50.6 (C9a), between δ 2.89 (C4−*H*H), 3.47 (C3−H*H*), and δ 33.1 (*C*3a), and between δ 3.04 (C9a−*H*) and δ 61.6 (*C*9). IR (KBr) 2984, 2918, 1749, 1726, 1686, 1613, 1483, 1431, 1254, 1191, 1138, 1023 cm^{-1}; MS (FAB) *m/z* 502 ([M + Na]$^+$), 480 ([M +H]$^+$); HRMS (FAB) *m/z* [M + H]$^+$ 480.2026 (calcd for C$_{27}$H$_{30}$NO$_7$ 480.2022), [M + Na]$^+$ 502.1856 (calcd for C$_{27}$H$_{29}$NO$_7$Na 502.1842). Anal. Calcd for C$_{27}$H$_{29}$NO$_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.58; H, 6.12; N, 2.89.

7m: (1 mmol scale, 282 mg, 57%); R$_f$ = 0.4 (hexane−ether = 1:8); colorless crystals; mp 128−129.5 °C (AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.23 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 2.53 (ddddd, *J* = 12.9, 12.1, 9.8, 7.5, 5.1 Hz, 1H), 2.86 (dd, *J* = 16.6, 12.1 Hz, 1H), 3.05 (d, *J* = 12.9 Hz, 1H), 3.05 (dd, *J* = 9.8, 9.3 Hz, 1H), 3.08 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.46 (dd, *J* = 9.3, 7.5 Hz, 1H), 4.13 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.27−4.51 (m, 6H), 4.68 (d, *J* = 14.8 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.26−7.36 (m, 5H), 7.89 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.10 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 14.3 (CH$_3$), 32.3 (CH), 34.3 (CH$_2$), 46.5 (CH$_2$), 50.2 (CH), 50.3 (CH$_2$), 60.4 (C), 61.0 (CH$_2$), 62.1 (CH$_2$), 62.7 (CH$_2$), 127.6 (CH), 128.2 (CH), 128.7 (CH), 128.85 (CH), 128.92 (C), 129.8 (CH), 132.1 (CH), 134.5 (C), 136.7 (C), 140.6 (C), 166.1 (C), 168.2 (C), 170.4 (C), 171.6 (C); ^{1}H NMR (400 MHz, CD$_3$CN) δ (ppm) 1.16 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 2.44 (ddddd, *J* = 13.1, 11.9, 9.6, 7.4, 5.3 Hz, 1H), 2.89 (dd, *J* = 16.8, 11.9 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 3.11 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.11 (dd, *J* = 16.8, 5.3 Hz, 1H), 3.47 (dd, *J* = 9.2, 7.4 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.18−4.39 (m, 6H), 4.62 (d, *J* = 15.0 Hz, 1H), 7.28−7.33 (m, 4H), 7.35−7.39 (m, 2H), 7.87 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.95 (d, *J* = 1.8 Hz, 1H). Selected NOEs are between δ 2.44 (C3a−*H*) and δ 3.47 (C3−H*H*), and between δ

2.89 (C4−HH) and δ 3.04 (C9a−H). ^{13}C NMR (100.6 MHz, CD$_3$CN) δ (ppm) 14.9 (CH$_3$), 15.0 (CH$_3$), 15.2 (CH$_3$), 33.8 (CH), 35.3 (CH$_2$), 47.4 (CH$_2$), 51.2 (CH), 51.7 (CH$_2$), 62.2 (C), 62.5 (CH$_2$), 63.4 (CH$_2$), 63.8 (CH$_2$), 128.9 (CH), 129.4 (CH), 130.0 (CH), 130.2 (CH), 131.9 (CH), 133.0 (CH), 136.4 (C), 139.1 (C), 143.3 (C), 167.3 (C), 169.7 (C), 172.0 (C), 172.8 (C). Selected HMBC correlations are between δ 2.89 (C4−HH) and δ 51.7 (C3), between δ 3.47 (C3−HH), 2.89 (C4−HH), and δ 51.2 (C9a), between δ 2.89 (C4−HH), 3.04 (C9a−H), 3.47 (C3−HH), and δ 33.8 (C3a), and between δ 3.04 (C9a−H) and δ 62.2 (C9). IR (KBr) 2983, 1728, 1611, 1482, 1443, 1366, 1280, 1259, 1193, 1027 cm^{-1}; MS (EI) m/z 493 (M$^+$, 100), 390 (72), 91 (55%); HRMS (EI) m/z M$^+$ 493.2094 (calcd for C$_{28}$H$_{31}$NO$_7$ 493.2101).

7n: (0.5 mmol scale, 125 mg, 51%); R$_f$ = 0.7 (ether); colorless crystals; mp 124−125 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.54 (ddddd, J = 14.1, 12.2, 9.8, 7.5, 5.3 Hz, 1H), 2.87 (dd, J = 16.5, 12.2 Hz, 1H), 3.04 (d, J = 14.1Hz, 1H), 3.06 (dd, J = 9.8, 9.3 Hz, 1H), 3.08 (dd, J = 16.5, 5.3Hz, 1H), 3.47 (dd, J = 9.3, 7.5 Hz, 1H), 4.13 (dq, J = 10.7, 3.1 Hz, 1H), 4.26−4.47 (m, 4H), 4.69 (d, J = 14.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.27− 7.37 (m, 5H), 7.48 (dd, J = 8.0, 1.4 Hz, 1H), 7.67 (bs, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.8 (CH$_3$), 14.1 (CH$_3$), 32.4 (CH), 34.2 (CH$_2$), 46.5 (CH$_2$), 50.2 (CH), 50.3 (CH$_2$), 60.4 (C), 62.3 (CH$_2$), 62.8 (CH$_2$), 124.0 (C, q, J_{CF} = 272 Hz), 124.7 (CH, q, J_{CF} = 3.8 Hz), 127.6 (CH), 127.9 (CH, q, J_{CF} = 3.8 Hz), 128.2 (CH), 128.8 (CH), 128.9 (C, q, J_{CF} = 33 Hz), 130.3 (CH), 134.9 (C), 136.6 (C), 139.7 (C), 167.9 (C), 170.2 (C), 171.4 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) 62.71; ^{1}H NMR (400 MHz, CD3CN) δ (ppm) 1.16 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.46 (ddddd, J = 13.1, 12.1, 9.6, 7.4, 5.1 Hz, 1H), 2.91 (dd, J = 16.8, 12.1 Hz, 1H), 3.05 (d, J = 13.1 Hz, 1H), 3.12 (dd, J = 9.6, 9.2 Hz, 1H), 3.12 (dd, J = 16.8, 5.1 Hz, 1H), 3.48 (dd, J = 9.2, 7.4 Hz, 1H), 4.07 (dq, J = 10.7, 7.0 Hz, 1H), 4.18−4.37 (m, 4H), 4.63 (d, J = 15.0 Hz, 1H), 7.28−7.40 (m, 6H), 7.58 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H). Selected NOEs are between δ 2.46 (C3a−H) and δ 3.48 (C3−HH), and between δ 2.91 (C4−HH) and δ 3.05 (C9a−H). ^{13}C NMR

(100.6 MHz, CD$_3$CN) δ (ppm) 14.1 (CH$_3$), 14.3 (CH$_3$), 33.1 (CH), 34.5 (CH$_2$), 46.7 (CH$_2$), 50.5 (CH), 51.0 (CH$_2$), 61.5 (C), 62.9 (CH$_2$), 63.2 (CH$_2$), 125.2 (C, q, J_{CF} = 271 Hz), 125.4 (CH, q, J_{CF} = 3.8 Hz), 128.2 (CH, q, J_{CF} = 4.6 Hz), 128.3 (CH), 128.7 (C, q, J_{CF} = 32 Hz), 128.8 (CH), 129.6 (CH), 131.9 (CH), 136.3 (C), 138.4 (C), 142.2 (C), 168.8 (C), 171.1 (C), 172.0 (C). Selected HMBC correlations are between δ 2.91 (C4−*H*H) and δ 51.0 (*C*3), between δ 3.48 (C3−H*H*), 2.91 (C4−*H*H), and δ 50.5 (*C*9a), between δ 2.91 (C4−*H*H), 3.05 (C9a−*H*), 3.48 (C3−H*H*), and δ 33.1 (*C*3a), and between δ 3.05 (C9a−*H*) and δ 61.5 (*C*9). IR (KBr) 2927, 1747, 1726, 1699, 1334, 1261, 1162, 1128 cm^{-1}; MS (EI) *m/z* 489 (M$^+$, 25), 386 (15), 333 (14), 242 (29), 226 (36), 200 (100%); HRMS (EI) *m/z* M$^+$ 489.1772 (calcd for C$_{26}$H$_{26}$F$_3$NO$_5$ 489.1763).

3n: (0.5 mmol scale, 14 mg, 6%); R$_f$ = 0.4 (ether); colorless crystals; mp 164−165 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.30 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.36 (ddd, J = 10.9, 6.6, 5.9 Hz, 1H), 2.64 (d, J = 10.9 Hz, 1H), 3.33 (dd, J = 10.9, 5.9 Hz, 1H), 3.82 (d, J = 14.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 4.03−4.16 (m, 2H), 4.24−4.37 (m, 3H), 5.00 (d, J = 14.3 Hz, 1H), 6.79 (d, J = 8.1 Hz, 2H), 7.30−7.32 (m, 2H), 7.40−7.44 (m, 3H), 7.49 (d, J = 8.1 Hz, 2H). Selected NOEs are between δ 2.36 (C5−*H*) and δ 3.33 (C4−H*H*), 6.79 (Ar-*H*), 3.91 (C1−*H*) and between δ 3.33 (C4−H*H*) and δ 3.91 (C1−*H*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.5 (CH$_3$), 15.0 (CH$_3$), 36.3 (CH), 41.1 (CH), 44.4 (CH$_2$), 46.3 (CH$_2$), 60.1 (CH$_2$), 65.0 (CH$_2$), 79.0 (CH), 79.7 (C), 123.8 (C, q, J_{CF} = 272 Hz), 125.7 (CH, q, J_{CF} = 3.8 Hz), 127.7 (CH), 128.1 (CH), 129.1 (CH), 129.2 (CH), 131.3 (C, q, J_{CF} = 33 Hz), 136.7 (C), 140.7 (C), 162.7 (C), 167.1 (C), 172.8 (C). Selected HMBC correlations are between δ 2.36 (C5−*H*), 2.64 (C4−*H*H), 3.91 (C1−*H*), and δ 172.8 (*C*2), between δ 2.36 (C5−*H*), 2.64 (C4−*H*H), 3.33 (C4−H*H*), 3.91 (C1−*H*), and δ 79.0 (*C*6), between δ 2.64 (C4−*H*H) and δ 41.1 (*C*1), and between δ 2.64 (C4−*H*H), 3.91 (C1−*H*), and δ 36.3 (*C*5). ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −62.85; IR (KBr) 2984, 2931, 1699, 1668, 1621, 1327, 1164, 1124, 1068, 1020 cm^{-1}; MS (EI) *m/z* 489 (M$^+$, 21), 291 (43), 205 (92), 200 (63), 91 (100%); HRMS (EI) *m/z* M$^+$ 489.1789 (calcd for C$_{26}$H$_{26}$F$_3$NO$_5$ 489.1763).

13i: (1 mmol scale, 261 mg, 57%, including a small amount of impurity); R_f = 0.5 (hexane−ether = 1:2); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1:1) δ (ppm) 3.95 (dd, J = 6.2, 1.4 Hz, 2H × 0.5), 4.20 (dd, J = 6.6, 1.0 Hz, 2H × 0.5), 4.50 (s, 2H × 0.5), 4.74 (s, 2H × 0.5), 5.90 (dt, J = 15.6, 6.2 Hz, 1H × 0.5), 6.06 (dt, J = 15.6, 6.6 Hz, 1H × 0.5), 6.95 (d, J = 15.6 Hz, 1H × 0.5), 6.98 (d, J = 15.6 Hz, 1H × 0.5), 7.15 (s, 1H × 0.5), 7.23−7.54 (m, 7H+1H × 0.5), 7.58−7.62 (m, 1H), 7.98 (dd, J = 8.2, 1.2 Hz, 1H × 0.5), 8.00 (dd, J = 8.2, 1.2 Hz, 1H × 0.5); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 46.1 (CH$_2$), 47.7 (CH$_2$), 49.1 (CH$_2$), 51.1 (CH$_2$), 120.1 (C, q, J_{CF} = 275 Hz), 120.3 (C, broad q, J_{CF} = 275 Hz), 124.7 (CH), 123.45−124.46 (C, m), 124.8 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 128.95 (CH), 129.00 (CH), 129.1 (CH), 129.3 (CH), 130.35 (CH), 130.43 (CH), 131.9 (C), 132.3 (C), 133.5 (CH), 133.6 (CH), 134.5 (C), 135.7 (C), 136.0 (CH, m), 136.2 (CH, m), 147.59 (C), 147.63 (C), 162.6 (C), 162.7 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −66.43 (q, J_{FF} = 6.5 Hz), −66.65 (q, J_{FF} = 6.5 Hz), −69.89 (q, J_{FF} = 6.5 Hz), −69.99 (q, J_{FF} = 6.5 Hz); IR (neat) 3068, 3032, 2931, 1651, 1608, 1524, 1435, 1386, 1348, 1286, 1221, 1166, 985 cm^{-1}; MS (EI) m/z 458 (M$^+$, 3.8), 296 (28), 106 (34), 91 (100%); HRMS (EI) m/z 458.1057 (calcd for C$_{21}$H$_{16}$F$_6$N$_2$O$_3$ 458.1065).

Typical experimental procedure for Table 3-5 (entry 5). A solution of **13i** (261 mg, 0.57 mmol) in toluene (1.0 mL) was heated at 110 °C for 20 h. The mixture was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with hexane−ether as eluent to give **16i** (231 mg, 89%).

16i: (0.57 mmol scale, 231 mg, 89%); R_f = 0.2 (hexane−ether = 2:1); colorless crystals; mp 219−220 °C (AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.64 (ddddd, J = 13.5, 12.1, 9.6, 7.2, 4.3 Hz, 1H), 2.81 (dd, J = 13.5, 1.2 Hz, 1H), 2.95 (dd, J = 17.2, 12.1 Hz, 1H), 3.06 (dd, J = 9.6, 9.4 Hz, 1H), 3.12 (dd, J = 17.2, 4.3 Hz, 1H), 3.28 (dd, J = 9.4, 7.2 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 4.62 (d, J = 14.8 Hz, 1H), 7.25 (d-like, J = 7.4 Hz, 2H), 7.28−7.37 (m, 3H), 7.51 (dd, J = 8.4, 8.0 Hz, 1H), 7.90 (dd, J = 8.0, 1.2 Hz, 1H), 8.11 (d. J = 8.4 Hz, 1H). Selected NOEs are between

δ 2.64 (C3a−H) and δ 3.28 (C3−HH) and between δ 2.95 (C4−HH) and δ 2.81 (C9a−H). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 30.9 (CH$_2$), 32.4 (CH, q, J_{CF} = 2.3 Hz), 46.6 (CH), 47.2 (CH$_2$), 48.7 (CH$_2$), 56.9 (C, septet, J_{CF} = 27 Hz), 123.6 (C, q, J_{CF} = 288 Hz), 124.3 (C, q, J_{CF} = 285 Hz), 125.5 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 129.0 (CH), 129.5 (C), 132.9 (C), 135.5 (CH, septet, J_{CF} = 3.8 Hz), 136.0 (C), 151.1 (C), 167.4 (C). Selected HMBC correlations are between δ 3.28 (C3−HH) and 2.95 (C4−HH), between δ 46.6 (*C*9a), δ 2.95 (C4−HH), 3.28 (C3−HH), and δ 32.4 (*C*3a), and between δ 2.81 (C9a−H) and δ 56.9 (*C*9). ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −66.23 (q, J_{FF} = 6.9 Hz), −70.27 (q, J_{FF} = 6.9 Hz); IR (KBr) 3033, 2929, 1699, 1530, 1431, 1349, 1263, 1245, 1195, 1080 cm^{-1};MS (EI) *m/z* 458 (M$^+$, 71), 91 (100%); HRMS (EI) *m/z* 458.1064 (calcd for C$_{21}$H$_{16}$F$_6$N$_2$O$_3$ 458.1065). Anal. Calcd for C$_{21}$H$_{16}$F$_6$N$_2$O$_3$: C, 55.03; H, 3.52; N, 6.11. Found: C, 55.01; H, 3.55; N, 6.15.

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Chapter 4

Sequential Intramolecular Cyclization of Diarylpropenamines with Electron-Deficient Carboxylic Acids

4-1 Introduction

The intramolecular Diels-Alder reaction (IMDA) between alkenes and dienes is a powerful tool for the facile construction of multicyclic skeletons. [1] The IDMA reaction of vinyl benzene (styrene) as a diene requires relatively harsh conditions, because of involving dearomatization of benzene ring.[2]

In chapter 3, intramolecular [2 + 2] and [4 + 2] cycloaddition (IMDA) reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate with *E*-cinnamylamines under the amide formation conditions in sequential processes were described.[3] In addition to the cycloaddition reactions of styrenes, the inter- and intramolecular reactions of diarylethenes were studied.[2c, 4] Furthermore, one of the important selectivities of the IMDA reaction in general are formation of *trans*- or *cis*-fused ring,[1b,5] and the investigation on the stereoselectivity of the IMDA reaction of styrenes with various substituents is of considerable interest.[2c, 2k]

In this chapter, the sequential amide formation/IMDA/H$^+$-shift reactions of electron-deficient alkenyl carboxylic acids with *Z*-cinnamyl amines and various 3,3-diaryl-2-propen-1-amines have been studied. This reaction proceeds to give tricyclic compounds, functionalized hexahydrobenzo[*f*]isoindoles. Some biologically active compounds such as podophyllotoxin and 4-phenylbenzo[*f*]isoindoles have the skeletons of the [4 + 2] cycloaddition products of 3,3-diaryl-2-propen-1-amines. In order to understand the factors to

control *cis-* and *trans-*fused stereochemistry in the present results, DFT calculations have been carried out.

4-2 Results and Discussion

In chapter 3, reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and *E*-cinnamylamines bearing *p*-H, halogen and MeO groups in the presence of EDCI/HOBt/Et$_3$N at room temperature to give cyclobutane-fused pyrrolidines are described.[3] The products may be formed via amide formation/intramolecular [2 + 2] cycloaddition. First, reaction with *Z*-cinnamylamines has been examined. Reaction with benzyl or cyclohexylmethyl cinnamylamines **2a,b** (*Z:E* = ca. 5:1) in the presence of EDCI/HOBt/Et$_3$N in THF at room temperature gave a complex mixture and the possible [2 + 2] cycloadducts were not detected. The reaction at 80-110 °C gave [4 + 2] cycloadducts, *cis-*fused tricyclic compounds **3a,b** as the major products (Table 4-1). The *cis-*fused stereochemistry of **3a,b** was determined by NOEs in C$_6$D$_6$.

Table 4-1. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and *Z*-cinnamylamines **2**.
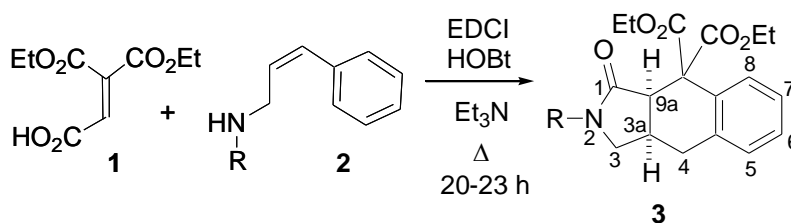
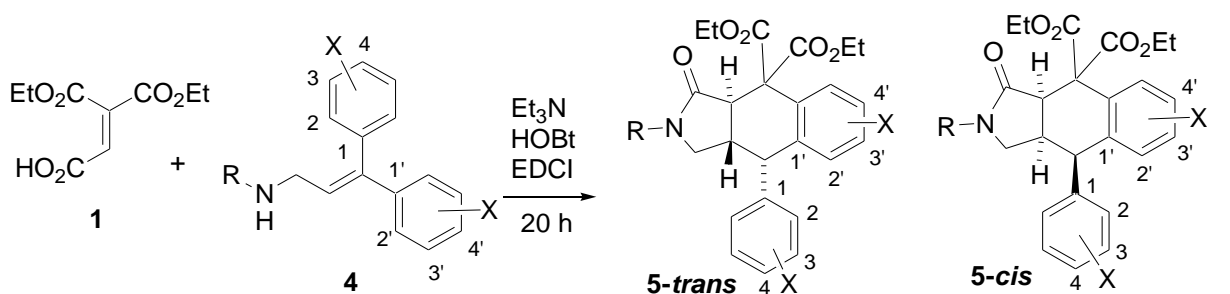| Entry	2	R	Solvent	Temp.	Product	Yield (%)
1	**2a**[a]	CH$_2$Ph	THF	r.t.	[b]	-
2	**2a**[a]	CH$_2$Ph	Benzene	80°C	**3a**	62
3	**2a**[a]	CH$_2$Ph	Toluene	110 °C	**3a**	58
4	**2b**[a]	CH$_2$Cyclohexyl	THF	r.t.	[b]	-
5	**2b**[a]	CH$_2$Cyclohexyl	Benzene	80 °C	**3b**	50
6	**2b**[a]	CH$_2$Cyclohexyl	Toluene	110 °C	**3b**	61

[a] *Z:E* = 5:1. [b] A complex mixture.

Next, the reaction of **1** and 3,3-diaryl-2-propenylamines **4** in the presence of the amide condensation reagents has been examined (Table 4-2). The influence of the second aromatic ring on stereochemistry by both steric and electronic effects is of mechanistic and synthetic interests.

3,3-Diaryl-2-propen-1-amines **4** were prepared from the corresponding alcohols.[6] The reaction of **1** and *N*-benzyl 3,3-diphenyl-2-propen-1-amine **4a** with EDCI/HOBt/Et$_3$N in THF at room temperature gave a complex mixture. However, the reaction in DMF gave *trans*-fused hexahydrobenzo[*f*]isoindole **5a-*trans*** in 52% yield via [4 + 2] cycloaddition. Interestingly, the reaction of **4a,b** in benzene or toluene at 80 or 110 °C gave *cis*-fused hexahydrobenzo[*f*]isoindoles **5a,b-*cis*** as major products. Similarly, the reaction of N-benzyl-3,3-bis(4-fluorophenyl)-2-propenylamine **4c** in DMF at room temperature gave *trans*-fused tricyclic product **5c-*trans*** in 53% yield and the reaction of **4c** in benzene or toluene at 80 or 110 °C gave *cis*-fused product **5c-*cis*** in 87 and 98% yields, respectively. On the other hand, reaction of **1** and 4,4'-dichloro and 3,3'-di(trifluoromethyl) derivatives **4d,e** in THF, DMF and benzene at room temperature, 80 and 110 °C gave *trans*-fused tricyclic products **5d,e-*trans*** in high yields. Product **5e-*trans*** from 3,3'-CF$_3$ substituted amine substrate 4e was obtained as a single regioisomer (3,3'-CF$_3$). The reaction of **1** and 4,4'-dimethyl derivative **4f** in DMF gave a complex mixture at room temperature and the reaction in DMF, benzene and toluene at 80 and 110 °C gave *cis*-fused tricyclic product **5f-*cis*** selectively. The relative configurations of **5** were determined by NOEs in CDCl$_3$ or C$_6$D$_6$. The reaction of **1** and 4,4'-dimethoxy derivative **4g** gave a complex mixture in THF, DMF, benzene and toluene at room temperature, 80 and 110 °C.

Thus, the reaction with 3,3-diaryl-2-propen-1-amines gave *cis*- and *trans*-fused tricyclic compounds selectively, depending on the substituents on the benzene ring, reaction temperature and solvent.

Table 4-2. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and

3,3-diaryl-2-propen-1-amines **4**.

Entry	**4**[a]	X	R	Solvent	Temp.	Product	Yield (%)
1	**4a**	H	CH$_2$Ph	THF	r.t.	[b]	-
2	**4a**	H	CH$_2$Ph	DMF[c]	r.t.	**5a-*trans***	52
3	**4a**	H	CH$_2$Ph	Benzene	80 °C	**5a-*cis***	48[d]
4	**4b**	H	CH$_2$Cyclohexyl	Benzene	80 °C	**5b-*cis***	55[d]
5	**4c**	4,4'-F	CH$_2$Ph	THF	r.t.	[e]	-
6	**4c**	4,4'-F	CH$_2$Ph	DMF[c]	r.t.	**5c-*trans***	53
7	**4c**	4,4'-F	CH$_2$Ph	Benzene	80 °C	**5c-*cis***	87
8	**4c**	4,4'-F	CH$_2$Ph	Toluene	110 °C	**5c-*cis***	98
9	**4d**	4,4'-Cl	CH$_2$Ph	THF	r.t.	**5d-*trans***	89
10	**4d**	4,4'-Cl	CH$_2$Ph	DMF[f]	r.t.	**5d-*trans***	93
11	**4d**	4,4'-Cl	CH$_2$Ph	Benzene	80 °C	**5d-*trans***	67
12	**4e**	3,3'-CF$_3$	CH$_2$Ph	THF	r.t.	**5e-*trans***	99
13	**4e**	3,3'-CF$_3$	CH$_2$Ph	DMF[f]	r.t.	**5e-*trans***	93
14	**4e**	3,3'-CF$_3$	CH$_2$Ph	Benzene	80 °C	**5e-*trans***	93
15	**4f**	4,4'-Me	CH$_2$Ph	Toluene	110 °C	**5f-*cis***	48[g]
16	**4f**	4,4'-Me	CH$_2$Ph	DMF	110 °C	**5f-*cis***	55

[a] The reaction of **4g** (X = 4,4'-OMe) gave a complex mixture. [b] A complex mixture. [c] The reaction in DMF at 80 or 110 °C gave a mixture of **5-*cis*** and **5-*trans***. [d] The reaction in toluene at 110 °C gave **5-*cis*** in lower yields (**5a-*cis*** 32%, **5b-*cis*** 26%) and a complex mixture. [e] A mixture containing **5c-*trans***. [f] The reaction in DMF at 80 or 110 °C also gave **5-*trans*** in 89-95% yields. [g] The reaction in benzene at 80 °C gave **5f-*cis*** in lower yield (17%) and a complex mixture.

To obtain some insights into the mechanism, the reactions with dissymmetrically substituted 3,3-diaryl-2-propen-1-amines have been studied (Table 4-3). Reaction of **1** with (*Z*) and (*E*)-3-(2- or 4-chlorophenyl)-3-phenyl-2-propen-1-amines **4h-j** in the presence of EDCI/HOBt/Et$_3$N at room temperature gave *trans*-fused hexahydrobenzo[*f*]isoindoles **5h,i,j-*trans*** stereoselectively in 30-86% yields (entries 1,2,5,6,11). At higher temperature in benzene or toluene, *cis*-fused hexahydrobenzo[*f*]isoindoles **5h,i,j-*cis*** were also formed (entries 3,4,8,9,13,14). Reaction of **1** with (*Z*)-3-(4-nitrophenyl)-3-phenyl-2-propen-1-amine **4k** in the presence of EDCI/ HOBt/Et$_3$N at 110 °C gave *trans*-fused hexahydrobenzo[*f*]isoindoles **5k-*trans*** as the major product in 55% yield. Highly electron-deficient NO$_2$ group on phenyl group may decrease the [4 + 2] cycloaddition reaction rate. Thus, *E*-substituted aryl group reacted selectively as a styrene component.

Next the reactions of other electron-deficient alkenes **6** with carboxyl group and 3,3-diaryl-2-propen-1-amines **4** were carried out in order to examine the generality of the reaction (Table 4-4). Reaction of *β*-substituted (CO$_2$Me, CF$_3$, bisCF$_3$) *α,β*-unsaturated carboxylic acids **6a-c** and 3,3-diaryl-2-propen-1-amines (Ar=Ph, C$_6$H$_4$-4-Cl) **4a,d** with EDCI/HOBt/Et$_3$N at room temperature gave the corresponding amides **7**. On the other hand, the reaction of **6a,c** and **4a**, **6a-c** and **4d** on heating (at 60-160 °C) gave *trans*-fused tricyclic compounds **8** as the major products.

Transformation of the amides **7** to the tricyclic compounds **8** was also examined. Thermal reaction of **7a,c,d,f** with and without acid or base gave **8** in 21-88% yields (Table 4-5).

In order to understand the reaction mechanism of the cycloadditions and find the factors to control *cis*- and *trans*-fused stereochemistry, a theoretical study was carried out by DFT calculation.[7] Some theoretical studies on *cis* and *trans*-fused stereoselectivity of IMDA reactions have been reported.[8c-f] The selectivity varies depending on the steric and electronic effects of linkers and substituents.

Table 4-3. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and dissymmetrically substituted 3,3-diaryl-2-propen-1-amines **4h-k**.
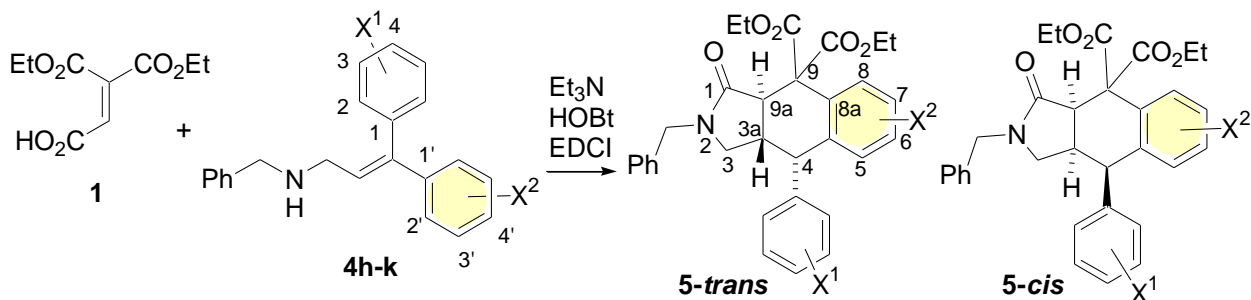
| Entry	4	X^1	X^2	Solvent	Temp.	5-*trans* (Yield %)	5-*cis* (Yield %)
1	**4h**	2-Cl	H	THF	r.t.	**5h-*trans*** (30)	
2	**4h**	2-Cl	H	DMF	r.t.	**5h-*trans*** (33)	
3	**4h**	2-Cl	H	Benzene	80 °C	**5h-*trans*** (18)[a]	**5h-*cis*** (32)[a]
4	**4h**	2-Cl	H	Toluene	110 °C	**5h-*trans*** (28)[a]	**5h-*cis*** (56)[a]
5	**4i**	4-Cl	H	THF	r.t.	**5i-*trans*** (59)	
6	**4i**	4-Cl	H	DMF	r.t.	**5i-*trans*** (72)	
7	**4i**	4-Cl	H	DMF	80 °C	**5i-*trans*** (58)	
8	**4i**	4-Cl	H	Benzene	80 °C	**5i-*trans*** (48)[a]	**5i-*cis*** (27)[a]
9	**4i**	4-Cl	H	Toluene	110 °C	**5i-*trans*** (5)[a]	**5i-*cis*** (39)[a]
10	**4j**	H	4'-Cl	THF	r.t.	**5j-*trans*** (-)[b]	
11	**4j**	H	4'-Cl	DMF	r.t.	**5j-*trans*** (86)	
12	**4j**	H	4'-Cl	DMF	80 °C	**5j-*trans*** (71)	
13	**4j**	H	4'-Cl	Benzene	80 °C	**5j-*trans*** (61)[a]	**5j-*cis*** (18)[a]
14	**4j**	H	4'-Cl	Toluene	110 °C	**5j-*trans*** (47)[a]	**5j-*cis*** (31)[a]
15	**4k**	4-NO$_2$	H	THF	r.t.	**5k-*trans*** (32)[c]	
16	**4k**	4-NO$_2$	H	DMF	r.t.	**5k-*trans*** (34)[c]	
17	**4k**	4-NO$_2$	H	Toluene	110 °C	**5k-*trans*** (55)	
18	**4k**	4-NO$_2$	H	DMF	110 °C	**5k-*trans*** (36)[d]	

[a] The yields were calculated by ^{1}H NMR. [b] A complex mixture containing a small amount of **5j-*trans***. [c] A complex mixture containing unidentified compounds was formed along with **5k-*trans***. [d] A small amount of possible phenyl epimer of **5k-*trans*** was also formed but could not be purified.

Table 4-4. Reactions of electron-deficient alkenes **6** and 3,3-diaryl-2-propen-1-amines **4**.
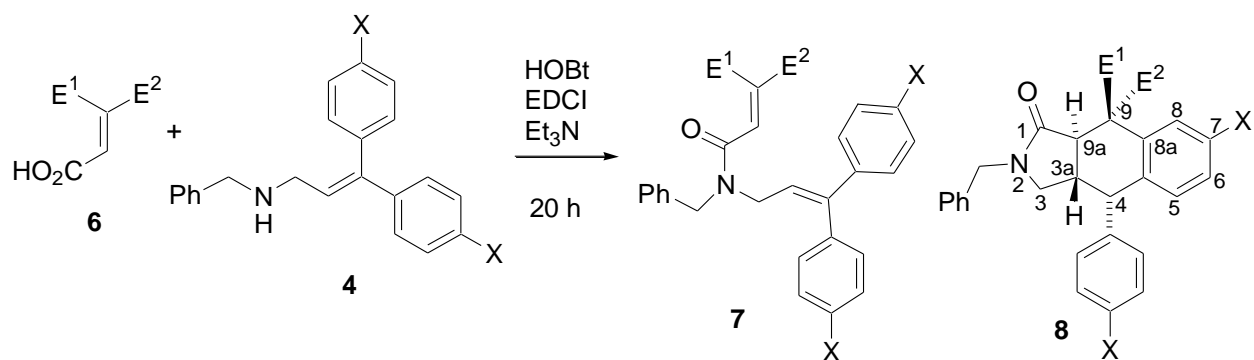
Entry	6	E^1	E^2	4	X	Solvent	Temp.	Product	Yield (%)
1	6a	H	CO$_2$Me	4a	H	THF	r.t.	7a[a]	ca. 77
2	6a	H	CO$_2$Me	4a	H	Toluene	110 °C	8a	47
3	6b	H	CF$_3$	4a	H	THF	r.t.	7b	89
4	6b	H	CF$_3$	4a	H	Xylene	140 °C	[c]	-
5	6b	H	CF$_3$	4a	H	Toluene[b]	160 °C	[c]	-
6	6c	CF$_3$	CF$_3$	4a	H	THF	r.t.	7c[a]	ca. 39
7	6c	CF$_3$	CF$_3$	4a	H	Benzene	80 °C	8c	37
8	6c	CF$_3$	CF$_3$	4a	H	Toluene	110 °C	8c	48
9	6a	H	CO$_2$Me	4d	Cl	THF	r.t.	7d[a]	ca. 86
10	6a	H	CO$_2$Me	4d	Cl	THF	60 °C	8d	80
11	6a	H	CO$_2$Me	4d	Cl	Benzene	80 °C	8d	75
12	6a	H	CO$_2$Me	4d	Cl	Toluene	110 °C	8d	69
13	6b	H	CF$_3$	4d	Cl	THF	r.t.	7e	77
14	6b	H	CF$_3$	4d	Cl	Toluene	110 °C	7e	67
15	6b	H	CF$_3$	4d	Cl	Xylene	140 °C	8e	27
16	6b	H	CF$_3$	4d	Cl	Toluene[b]	160 °C	8e	38
17	6c	CF$_3$	CF$_3$	4d	Cl	THF	r.t.	7f[a]	ca. 57
18	6c	CF$_3$	CF$_3$	4d	Cl	Benzene	80 °C	8f	53
19	6c	CF$_3$	CF$_3$	4d	Cl	Toluene	110 °C	8f	45

[a] Products **7a,c,d,f** are unstable and decompose to give complex mixtures gradually.
[b] In a closed vessel. [c] A complex mixture.

Table 4-5. Transformation of amides **7** to hexahydrobenzo[*f*]isoindoles **8**.
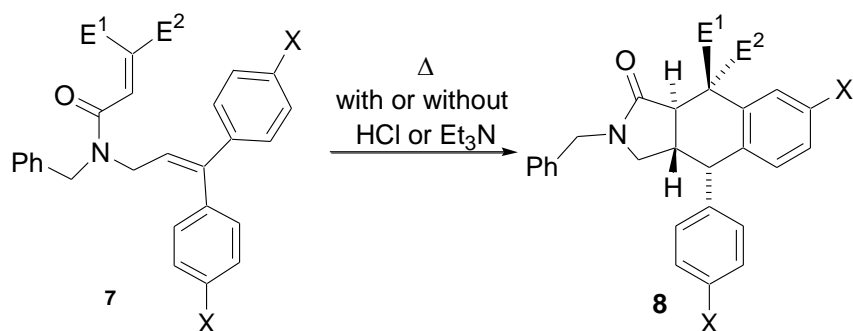
Entry	7	E^1	E^2	X	Solvent	Additive	Temp.	Product	Yield (%)
1	**7a**	H	CO_2Me	H	Toluene	none	110 °C	**8a**	21
2	**7a**	H	CO_2Me	H	Toluene	HCl (1 equiv)[a]	110 °C	**8a**	67
3	**7a**	H	CO_2Me	H	Toluene	Et₃N (1 equiv)	110 °C	**8a**	83
4	**7b**	H	CF_3	H	Toluene	none	110 °C	[b]	
5	**7b**	H	CF_3	H	Toluene	HCl (1 equiv)[a]	110 °C	[b]	
6	**7b**	H	CF_3	H	Toluene	Et₃N (1 equiv)	110 °C	[b]	
7	**7c**	CF_3	CF_3	H	Toluene	Et₃N (1 equiv)	110 °C	**8c**	55
8	**7d**	H	CO_2Me	Cl	THF	Et₃N (1 equiv)	60 °C	**8d**	88
9	**7e**	H	CF_3	Cl	Toluene	none	110 °C	[b]	
10	**7e**	H	CF_3	Cl	Toluene	HCl (1 equiv)[a]	110 °C	[b]	
11	**7e**	H	CF_3	Cl	Toluene	Et₃N (1 equiv)	110 °C	[b]	
12	**7f**	CF_3	CF_3	Cl	Toluene	Et₃N (1 equiv)	110 °C	**8f**	87

[a] 1M HCl in ether was added. [b] No reaction.

The *cis*- and *trans*-fused stereoselectivity for reaction of diaryl propenyl amides in the [4 + 2] cycloaddition path has been examined by DFT calculations (Scheme 4-1). For formation of *trans*-fused [4 + 2] cycloadduct **CM1-*trans***, the asynchronous and concerted path for X = H was obtained. For formation of *cis*-fused [4 + 2] cycloadduct **CM2-*cis***, stepwise path via zwitter-ionic intermediate **BM2-*cis*** was obtained. The activation energy TSa (+21.47 kcal/mol) leading to **CM1-*trans*** is lower than TSb (+22.51 kcal/mol) and TSc (+24.06 kcal/mol) leading to **CM2-*cis***. However, the cycloadduct **CM2-*cis*** (+5.96 kcal/mol) is more stable than **CM1-*trans*** (+11.03 kcal/mol). The stability of **CM2-*cis*** may be partially attributed to **8a,9a-*cis*** (1,3-diequatorial-like)

conformation of the cyclohexene ring. At higher temperature, the reaction leads to the more stable [4 + 2] cycloadduct **CM2-*cis***. The path reacting with *Z*-phenyl group (via **AM3** → **BM3-*cis*** → **CM3-*cis***) was also calculated. However, the path to give **CM3-*cis*** with **8a,9a-*trans*** stereochemistry is unfavorable. The paths reacting with *Z*-phenyl group to give **9a-*trans*** stereochemistry could not be obtained because of the steric hindrance. Thus, the reaction paths at *E*-substituted phenyl group of diphenyl propenyl substrates as a diene moiety were preferentially obtained for both *trans* and *cis*-fused products by the DFT calculations. This is in agreement with the experimental results of reactions of dissymmetrically substituted diaryl-2-propen-1-amines **4h-k**.

The 1,3-H shift may not be a concerted process,[9] and the possible stepwise protonation-deprotonation (1,3-H$^+$ shift)[10] is also considered to play an important role to *cis*- and *trans*- fused stereoselectivity in these cases. Selective formation of the stereochemistry at the 4-aryl group may arise from the protonation from less hindered side (*cis* to adjacent H). The result is in agreement with predominant formation of *trans*-benz[*f*]isoindoline in the [4 + 2] cycloaddition reaction of *N*-allyl-*N*-diphenylallyl amide at 180 °C for 6 days reported by Oppolzer et al.[2c]

The reaction at room temperature proceeds favorably to give **CM1-*trans*** and the use of polar solvent such as DMF facilitates the stepwise protonation-deprotonation and leads to the *trans*-fused rearomatized product **5M-*trans***.

The reaction of bis(4-chlorophenyl) and bis(4-methylphenyl) substrate models (X = Cl, Me) were also calculated. In the reaction of bis(4-methylphenyl) substrate model (X = Me), the path via intermediate **BM1-*trans*** was obtained.

The stepwise 1,3-H$^+$ shift of **CM2-*cis*** (X = H and Me) by catalytic acid in situ leads to rearomatized **5M-*cis***. The path through TSb with partial ionic character and zwitter-ionic intermediate **BM2-*cis*** (X = Cl) is less stable than those of (X = H and Me) because of destabilization by electron-withdrawing chloro-substituents.

The observed difference on *cis*- and *trans*-fused selectivity by substituents (Table 4-2) may be correlated to the Hammet constants σ.[11] σ (*p*-Me; -0.07) gave *cis*-fused product. σ (H; 0, *p*-F; 0.06) gave *cis*- and *trans*-fused products depending on the reaction conditions. Positive values of σ (*p*-Cl; 0.23, m-CF$_3$; 0.43) only gave *trans*-fused cycloadducts. Larger negative value of σ (*p*-OMe; -0.27) gave a complex mixture, probably because of the formation of the byproducts. The selective formation of *trans*-fused ring of mono-NO$_2$-substituted **5k-*trans*** (Table 4-3) may be attributed to the destabilization of the cation intermediate **BM2-*cis*** similar to bis-Cl and CF$_3$-substituted substrates.
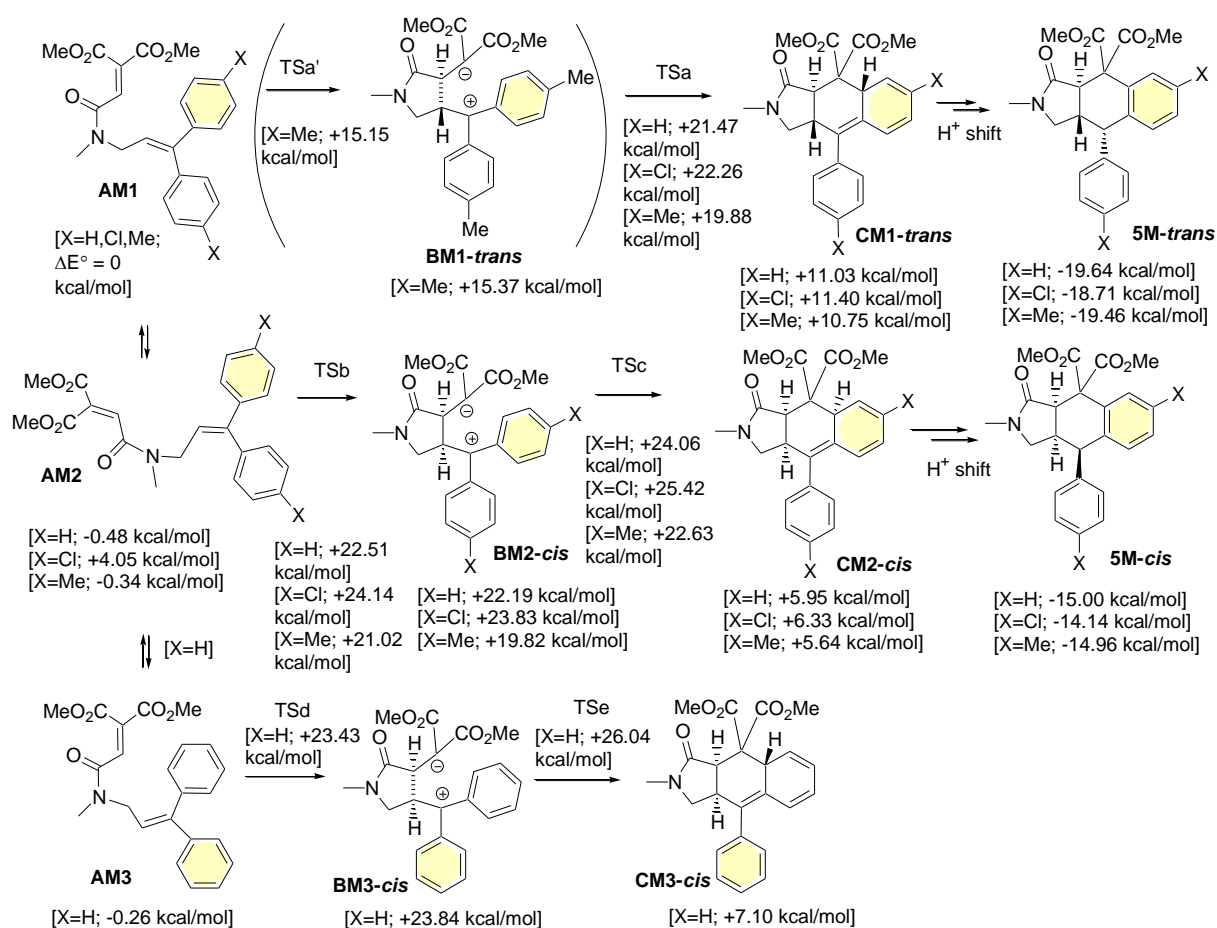
Scheme 4-1. [4 + 2] Cycloaddition reaction paths for model compounds of diaryl propenyl amides. ΔE's (sum of electronic and zero-point energies) by B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = THF) // B3LYP/6-31G* SCRF = (PCM, solvent = THF) relative to AM1 are shown.

Next, the [4 + 2] cycloaddition reaction path of less reactive methyl (2*E*)-4-amino-4-oxo-2-butenoates **7** has been examined (Scheme 4-2). For **7M**, the models of **7a,d**, the concerted paths lead to both *cis* and *trans* adducts. The activation energies of TSFa and TSFb for **7M** leading to cycloadducts **CMF-*trans*** and **CMF-*cis*** are substantially higher than those of TSa, TSb, and TSc in Scheme 4-2. The path with lower activation barrier TSFa may give *trans*-[4 + 2] cycloadduct **CMF-*trans*** and the final stable aromatic ring-reproduced product **8M-*trans*** by the stepwise protonation-deprotonation (1,3-H$^+$ shift) under the reaction conditions.
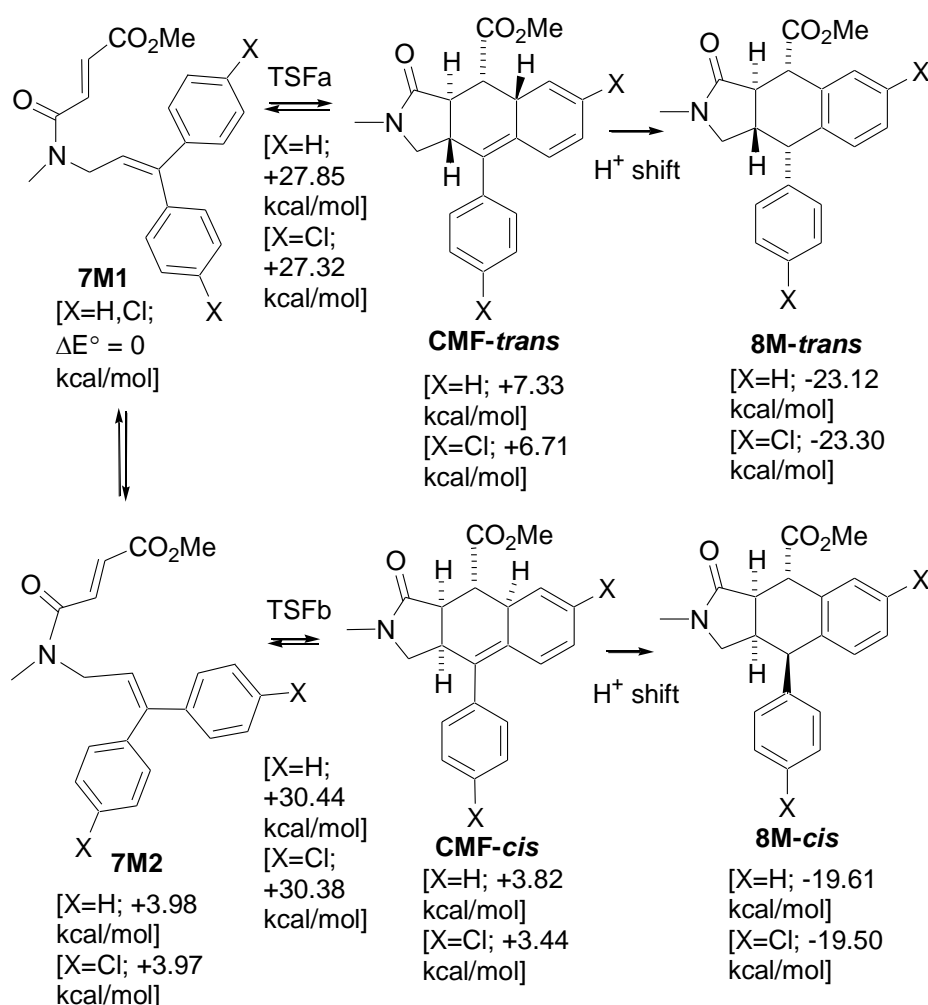
Scheme 4-2. [4 + 2] Cycloaddition reaction paths for the models of **7a,d**. ΔE's (sum of electronic and zero-point energies) by B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = THF) // B3LYP/6-31G* SCRF = (PCM, solvent = THF) are shown.

The reaction of less reactive amides **7a,c,d,f** with HCl or Et₃N has been shown to give the cyclized products. The 1,3-H$^+$ shift under thermal conditions without acid or base for **7a** may proceed intermolecularly as well. The [4 + 2] cycloaddition may be reversible and the catalysts accelerate the 1,3-H$^+$ shift step.

4-3 Conclusion

In summary, IMDA reactions of various 3,3-diarylpropenylamides of electron-deficient alkenes to give hexahydrobenzo[*f*]isoindoles were investigated. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with 3,3-diarylpropenylamines or *Z*-cinnamyl amines under the amide formation conditions gave the tricyclic compounds in sequential processes involving IMDA reaction. When the electron-withdrawing substituents (positive values of Hammet constants σ) are present on benzene ring, the [4 + 2] cycloaddition proceeds in *trans*-fused manner. When the substituents such as H and F (σ near 0) are present, the reaction gives *cis* and *trans*-fused products depending on the reaction conditions. When the substituents (slightly negative values of σ) are present, the reaction gives *cis*-fused product. These processes are controlled by the substituents on the benzene ring, reaction temperature, and solvent. Reaction of electron-deficient alkenic carboxylic acids such as fumarate and 3,3-diaryl-2-propen-1-amines under the amide formation conditions at room temperature gave the corresponding amides, and the reaction on heating gave *trans*-fused hexahydrobenzo[*f*]isoindoles. The origin of observed stereoselectivity of the fused rings has been examined by the DFT calculations.

4-4 Experimental Section

General Procedures

^{1}H Chemical shifts are reported in ppm relative to Me₄Si. ^{13}C Chemical shifts are reported in ppm relative to CDCl₃ (77.1 ppm). ^{19}F Chemical shifts are reported in ppm relative to CFCl₃. ^{13}C

multiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI, FAB or ESI. Mass analyzer type used for EI and FAB is double-focusing and that for ESI is TOF in the HRMS measurements. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75-150 μm).

1,1-Diethyl 2-hydrogen ethenetricarboxylate **1** was prepared according to the literature.[12] (*Z*)-Cinnamyl alcohol[13] was prepared by hydrogenation of 3-phenyl-2-propyn-1-ol with Lindlar catalyst in methanol.

(*Z*)-Cinnamyl bromide[14] was prepared by reaction of (*Z*)-cinnamyl alcohol with PBr_3 and pyridine in ether and used without further purification. (*Z*)-Cinnamylamines **2a-b** were prepared by reaction of benzylamine or cyclohexylamine (2 equiv) with (*Z*)-cinnamyl bromide in ether according to the literature procedure.[15]

(*Z*)-Benzyl cinnamylamine (2a): *Z:E* = 5:1 (2.4 mmol scale, 274 mg, 51%); R_f = 0.1 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) For the major isomer, 1.68 (bs, 1H), 3.55 (dd, J = 6.6, 1.9 Hz, 2H), 3.77 (s, 2H), 5.65 (dt, J = 11.6, 6.6 Hz, 1H), 6.53 (d, J = 11.6 Hz, 1H), 7.19-7.37 (m, 10H). Selected NOEs are between δ 5.65 (=C-H) and δ 6.53 (=C-H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) For the major isomer, 46.99 (CH2), 53.53 (CH2), 126.93 (CH), 127.01 (CH), 128.19 (CH), 128.27 (CH), 128.41 (CH), 128.80 (CH), 130.78 (CH), 130.94 (CH), 137.07 (C), 140.04 (C); IR (neat) 3313, 3024, 2831, 1599, 1494, 1453, 1115, 1028 cm^{-1}; MS (EI) *m/z* 223 (M[+], 35), 222 (17), 132 (100%); HRMS (EI) *m/z* 223.1372 (calcd for $C_{16}H_{17}N$ 223.1361).

(*Z*)-Cinnamyl cyclohexylmethylamine (2b): *Z:E* = 5:1 (20 mmol scale, 2.24 g, 49%); R_f = 0.4 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) For the major isomer, 0.834-0.957 (m, 2H), 1.08-1.29 (m, 3H), 1.36-1.48 (m, 1H), 1.62-1.77 (m, 5H), 2.43 (d, J = 6.6 Hz, 2H), 3.50 (dd, J = 6.5, 1.9 Hz, 2H), 5.76 (dt, J = 11.7, 6.5 Hz, 1H), 6.49 (d, J = 11.7 Hz, 1H), 7.16-7.37 (m, 5H). Selected NOEs are between δ 5.76 (=C-*H*) and δ 6.49 (=C-*H*) and between δ 3.50 (*CH2*) and δ 7.16-7.37 (Ph).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) For the major isomer,

26.03 (CH$_2$), 26.66 (CH$_2$), 31.45 (CH$_2$), 38.01 (CH), 47.92 (CH$_2$), 56.48 (CH$_2$), 126.76 (CH), 128.08 (CH), 128.74 (CH), 130.14 (CH), 131.56 (CH), 137.18 (C); IR (neat) 3323, 3023, 2923, 1600, 1494, 1447, 1124 cm^{-1}; MS (EI) m/z 229 (M$^+$, 9.3), 146 (19), 117 (100%); HRMS (EI) m/z 229.1836 (calcd for C$_{16}$H$_{23}$N 229.1830).

Typical experimental procedure for preparation 3 (Table 4-1, entry2). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF$_3$CO$_2$H (4 mL))[12] in benzene (0.7 mL) were added Z-benzyl cinnamylamine (**2a**) (223 mg, 1 mmol) in benzene (0.7 mL), Et$_3$N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol), and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and then heated at 80 °C and stirred for 20 h. The reaction mixture was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **3a** (261 mg, 62%).

3a: R$_f$ = 0.5 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 1.17 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 2.34 (dd, J = 17.4, 11.1 Hz, 1H), 2.86-2.98 (m, 3H), 3.49 (dd, J = 8.5, 8.5 Hz, 1H), 3.59 (d, J = 11.1 Hz, 1H), 4.07-4.26 (m, 2H), 4.27 (d, J = 14.7 Hz, 1H), 4.35-4.40 (m, 2H), 4.67 (d, J = 14.7 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 7.15-7.18 (m, 2H), 7.20-7.30 (m, 5H), 7.53 (dd, J = 7.7, 1.3 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.80 (CH$_3$), 13.99 (CH$_3$), 29.05 (CH), 33.21 (CH$_2$), 46.85 (CH$_2$), 48.41 (CH), 52.48 (CH$_2$), 60.72 (C), 61.72 (CH$_2$), 62.29 (CH$_2$), 126.96 (CH), 127.34 (CH), 127.77 (CH), 127.82 (CH), 127.97 (CH), 128.22 (CH), 128.49 (CH), 135.36 (C), 136.14 (C), 136.35 (C), 168.81 (C), 169.88 (C), 172.77 (C); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.843 (t, J = 7.1 Hz, 3H), 0.949 (t, J = 7.1 Hz, 3H), 2.09

(dd, J = 14.8, 8.6 Hz, 1H), 2.35 (ddddd, J = 11.5, 9.0, 8.6, 7.2, 6.4 Hz, 1H), 2.50 (dd, J = 14.8, 7.2 Hz, 1H), 2.58 (dd, J = 9.0 Hz, 6.4 Hz, 1H), 2.88 (dd, J = 9.0, 9.0 Hz, 1H), 3.62 (d, J = 11.5 Hz, 1H), 3.81-3.89 (m, 1H), 4.01-4.17 (m, 3H), 4.17 (d, J = 14.8 Hz, 1H), 4.35 (d, J = 14.8 Hz, 1H), 6.78 (d, J = 7.0 Hz, 1H), 6.93-7.08 (m, 7H), 7.83 (dd, J = 7.8, 1.0 Hz, 1H). Selected NOEs are between δ 2.35 (C3a-H) and δ 3.62 (C9a-H), 2.88 (C3-HH) and 2.50 (C4-HH). Atom numbering is shown in Table 4-1.; ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.85 (CH$_3$), 13.95 (CH$_3$), 29.30 (CH), 33.24 (CH$_2$), 46.94 (CH$_2$), 48.68 (CH), 52.21 (CH$_2$), 61.08 (C), 61.61 (CH$_2$), 62.17 (CH$_2$), 127.13 (CH), 127.38 (CH), 127.89 (CH), 128.24 (CH), 128.49 (CH), 128.66 (CH), 128.73 (CH), 136.15 (C), 136.78 (C), 137.29 (C), 168.87 (C), 169.95 (C), 172.26 (C). Selected HMBC correlations are between δ 2.35 (C4-HH), 2.50 (C4-HH), 2.58 (C3-HH), 2.88 (C3-HH), 3.62 (C9a-H) and δ 29.30 (C3a), δ 2.58 (C3-HH), 2.88 (C3-HH), 3.62 (C9a-H), 6.78 (C5-H) and δ 33.24 (C4), and between δ 3.62 (C9a-H) and δ 61.08 (C9).; IR (neat) 2980, 1734, 1689, 1485, 1444, 1247, 1096, 1031 cm^{-1}; MS (EI) m/z 421 (M$^+$, 45), 347 (8.4), 303 (14), 301 (12), 91 (100%); HRMS (EI) m/z 421.1906 (calcd for $C_{25}H_{27}NO_5$ 421.1889).

3b: (1 mmol scale, toluene, 110 °C, 262 mg, 61%); R$_f$ = 0.3 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 0.803-0.925 (m, 2H), 1.09-1.20 (m, 3H), 1.17 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.43-1.70 (m, 6H), 2.40 (dd, J = 17.5, 11.0 Hz, 1H), 2.87 (dd, J = 13.5, 6.7 Hz, 1H), 2.96-3.01 (m, 2H), 3.05 (dd, J = 9.0, 5.9 Hz, 1H), 3.30 (dd, J = 13.5, 7.8 Hz, 1H), 3.55 (d, J = 10.7 Hz, 1H), 3.66 (dd, J = 9.0, 8.6 Hz, 1H), 4.08-4.26 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 7.11-7.13 (m, 1H), 7.20-7.28 (m, 2H), 7.54-7.57 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.83 (CH$_3$), 13.98 (CH$_3$), 25.77 (CH$_2$), 25.83 (CH$_2$), 26.38 (CH$_2$), 29.17 (CH), 30.74 (CH$_2$), 30.78 (CH$_2$), 33.34 (CH$_2$), 35.85 (CH), 48.52 (CH), 49.40 (CH$_2$), 54.10 (CH$_2$), 60.54 (C), 61.65 (CH$_2$), 62.24 (CH$_2$), 126.94 (CH), 127.71 (CH), 127.95 (CH), 127.97 (CH), 135.36 (C), 136.14 (C), 168.75 (C), 169.90 (C), 172.96 (C); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.689-0.850 (m, 2H), 0.965-1.12 (m, 3H), 0.938 (t, J = 7.1 Hz, 3H), 0.993 (t, J = 7.0 Hz, 3H),

1.36-1.45 (m, 2H), 1.49-1.63 (m, 4H), 2.26 (dd, J = 14.8, 8.2 Hz, 1H), 2.53 (ddddd, J = 11.3, 8.8, 8.2, 7.0, 6.4 Hz, 1H), 2.69 (dd, J = 14.8, 7.0 Hz, 1H), 2.73 (dd, J = 9.0, 6.4 Hz, 1H), 2.90 (dd, J = 13.5, 6.8 Hz, 1H), 3.04 (dd, J = 9.0, 8.8 Hz, 1H), 3.12 (dd, J = 13.5, 7.2 Hz, 1H), 3.71 (d, J = 11.3 Hz, 1H), 3.91-3.99 (m, 1H), 4.07-4.24 (m, 3H), 6.92 (d, J = 7.4, 0.6 Hz, 1H), 7.05 (ddd, J = 7.6, 7.4, 1.2 Hz, 1H), 7.14 (ddd, J = 7.8, 7.6, 1.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H). Selected NOEs are between δ 2.53 (C3a-H) and δ 3.71 (C9a-H), 3.04 (C3-HH) and 2.69 (C4-HH).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 13.85 (CH$_3$), 13.90 (CH$_3$), 26.15 (CH$_2$), 26.70 (CH$_2$), 29.43 (CH), 30.88 (CH$_2$), 31.06 (CH$_2$), 33.44 (CH$_2$), 36.16 (CH), 48.76 (CH), 49.47 (CH$_2$), 53.77 (CH$_2$), 60.88 (C), 61.53 (CH$_2$), 62.10 (CH$_2$), 127.14 (CH), 127.76 (CH), 128.24 (CH), 128.98 (CH), 136.10 (C), 136.71 (C), 168.76 (C), 169.93 (C), 172.34 (C). Selected HMBC correlations are between δ 2.26 (C4-HH), 2.69 (C4-HH), 2.73 (C3-HH), 3.04 (C3-HH), 3.71 (C9a-H) and δ 29.30 (C3a), δ 2.58 (C3-HH), 2.88 (C3-HH), 3.62 (C9a-H), 6.92 (C5-H) and δ 29.43 (C4), and between δ 3.62 (C9a-H) and δ 60.88 (C9).; IR (neat) 2925, 2852, 1733, 1690, 1485, 1448, 1366, 1236, 1118, 1095, 1035 cm^{-1}; MS (EI) m/z 427 (M$^+$, 9.9), 345 (11), 117 (10), 84 (100%); HRMS (EI) m/z 427.2368 (calcd for C$_{25}$H$_{33}$NO$_5$ 427.2359).

Arylpropenyl esters, ethyl 3,3-diphenylacrylate **Xa** (for **4a-b**), ethyl 3,3-bis-(4-fluorophenyl)acrylate **Xc** (for **4c**), ethyl 3,3-bis-(4-chlorophenyl)acrylate **Xd** (for **4d**), ethyl 3,3-bis[3-(trifluoromethyl)-phenyl]acrylate **Xe** (for **4e**) and ethyl (2Z)-3-(2-chlorophenyl)-3-phenylprop-2-enoate **Xh** (for **4h**) and the corresponding alcohols, 3,3-diphenylprop-2-en-1-ol **Ya**, 3,3-bis(4-fluorophenyl)prop-2-en-1-ol **Yc**, 3,3-bis(4-chlorophenyl)prop-2-en-1-ol **Yd**, 3,3-bis[3-(trifluoromethyl)phenyl]prop-2-en-1-ol **Ye**, and 3-(2-chlorophenyl)-3-phenylprop-2-en-1-ol **Yh** were prepared according to the literature. [6] Arylpropenyl esters **Xf** (for **4f**), **Xg** (for **4g**), **Xi** (for **4i**), **Xj** (for **4j**), **Xk** (for **4k**) and the corresponding alcohols **Yf** (for **4f**), **Yg** (for **4g**), **Yi** (for **4i**), **Yk** (for **4k**) were prepared by the literature methods.[6]

The stereochemistry of ethyl 3-(2-chlorophenyl)-3-phenylprop-2-enoate **Xh** obtained as the major product by the literature method was reported as E^6 but it was found to be Z by the observed NOE's in C_6D_6. The ^1H NMR spectra of **Xh** in $CDCl_3$ were in accord with the reported data.

(2E)-3-(4-chlorophenyl)-3-phenylprop-2-en-1-ol (**Yj**) (for **4j**) was prepared by the Suzuki cross-coupling reaction of (E)-3-bromo-3-phenylprop-2-en-1-ol and 4-chlorophenylboronic acid by the literature method. [16]

Ethyl 3,3-bis(4-methylphenyl)acrylate (Xf): (2.7 mmol scale, 721 mg, 95%); $R_f = 0.4$ (hexane-ether = 4 : 1); pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, $J = 7.1$ Hz, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 4.06 (q, $J = 7.1$ Hz, 2H), 6.30 (s, 1H), 7.08-7.12 (m, 4H), 7.17-7.20 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.13 (CH_3), 21.29 (CH_3), 21.44 (CH_3), 59.96 (CH_2), 116.22 (CH), 128.38 (CH), 128.59 (CH), 129.09 (CH), 129.21 (CH), 136.16 (C), 137.94 (C), 138.34 (C), 139.61 (C), 156.94 (C), 166.31 (C); IR (neat) 2980, 1723, 1604, 1508, 1368, 1264, 1160, 1038 cm^{-1}; MS (EI) m/z 280 (M$^+$, 98), 235 (100%); HRMS (EI) m/z 280.1459 (calcd for $C_{19}H_{20}O_2$ 280.1463).

Ethyl 3,3-bis(4-methoxyphenyl)acrylate (Xg): (2.7 mmol scale, 537 mg, 64%); $R_f = 0.4$ (hexane-ether = 1 : 1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.16 (t, $J = 7.1$ Hz, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.07 (q, $J = 7.1$ Hz, 2H), 6.23 (s, 1H), 6.84 (d-like, $J = 9.0$ Hz, 2H), 6.91 (d-like, $J = 8.7$ Hz, 2H), 7.15 (d-like, $J = 8.7$ Hz, 2H), 7.24 (d-like, $J = 9.0$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.21 (CH_3), 55.27 (CH_3), 55.39 (CH_3), 59.90 (CH_2), 113.26 (CH), 113.74 (CH), 114.97 (CH), 130.04 (CH), 130.91 (CH), 131.33 (C), 133.89 (C), 156.43 (C), 159.71 (C), 160.79 (C), 166.50 (C); IR (neat) 2979, 2837, 1717, 1600, 1513, 1250, 1174, 1149, 1034 cm^{-1}; MS (EI) m/z 312 (M$^+$, 100), 267 (33), 240 (49%); HRMS (EI) m/z 312.1357 (calcd for $C_{19}H_{20}O_4$ 312.1362).

Ethyl (2Z)-3-(2-chlorophenyl)-3-phenylprop-2-enoate (Xh): ^1H NMR (400 MHz, C_6D_6) δ (ppm) 0.824 (t, $J = 7.1$ Hz, 3H), 3.88 (q, $J = 7.1$ Hz, 2H), 6.61 (s, 1H), 6.86 (ddd, $J = 7.6, 7.5, 2.0$

Hz, 1H), 6.91 (ddd, J = 7.5, 7.4, 1.4 Hz, 1H), 6.95-7.03 (m, 5H), 7.18-7.20 (m, 2H), 7.24 (dd, J = 7.6, 1.4 Hz, 1H). Selected NOEs are between δ 6.61 (C2-H) and δ 7.18-7.20 (2-H of Ph).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 13.99 (CH$_3$), 59.91 (CH$_2$), 119.56 (CH), 126.54 (CH), 127.67 (CH), 128.79 (CH), 129.05 (CH), 129.57 (CH), 130.62 (CH), 133.14 (C), 138.74 (C), 139.06 (C), 153.03 (C), 164.89 (C).

Xi and **Xj** were obtained as a ca. 1:1 mixture (20 mmol scale, 5.46 g, 95%). **Xi** (2.15 g, 38%) was partially isolated by fractional crystallization of the mixture (from hexane). **Xj** (3:1 (**Xj**:**Xi**) mixture) was obtained from the filtrates. The stereochemistries of **Xi** and **Xj** were assigned by the NOE's of the corresponding alcohols **Yi** and **Yj** obtained by DIBAL-H reduction. The spectral data for **Yj** obtained from **Xj** were in accord with those by the Suzuki cross-coupling reaction.

Ethyl (2Z)-3-(4-chlorophenyl)-3-phenylprop-2-enoate (Xi): R_f = 0.5 (hexane-ether = 4 : 1); colorless crystals; mp 67-68 °C (hexane); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.16 (t, δ = 7.1 Hz, 3H), 4.07 (q, J = 7.1 Hz, 2H), 6.37 (s, 1H), 7.15 (d-like, J = 8.4 Hz, 2H), 7.26-7.39 (m, 7H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.12 (CH$_3$), 60.27 (CH$_2$), 117.92 (CH), 128.24 (CH), 128.33 (CH), 128.56 (CH), 129.69 (CH), 130.69 (CH), 134.26 (C), 137.43 (C), 140.49 (C), 155.46 (C), 165.96 (C); IR (KBr) 2981, 1718, 1488, 1368, 1271, 1157, 1089 cm^{-1}; MS (EI) m/z 288 (M$^+$, 27), 286 (M$^+$, 81), 241 (100%); HRMS (EI) m/z 286.0759, 288.0732 (calcd for C$_{17}$H$_{15}$ClO$_2$ 286.0761, 288.0731); Anal. Calcd for C$_{17}$H$_{15}$ClO$_2$: C, 71.20; H, 5.27. Found: C, 71.27; H, 5.29.

Ethyl (2E)-3-(4-chlorophenyl)-3-phenylprop-2-enoate (Xj): R_f = 0.4 (hexane-ether = 4 : 1); pale yellow oil; (**Xj**:**Xi** = 3:1) ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.10 (t, J = 7.1 Hz, 3H), 4.04 (q, J = 7.1 Hz, 2H), 6.33 (s, 1H), 7.14-7.23 (m, 3H), 7.25-7.39 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.98 (CH$_3$), 60.14 (CH2), 117.81 (CH), 128.00 (CH), 128.61 (CH), 129.08 (CH), 129.55 (CH), 130.62 (CH), 135.50 (C), 138.51 (C), 139.26 (C), 155.10 (C), 165.86 (C); IR (neat) 2981, 1724, 1618, 1489, 1368, 1263, 1165, 1092 cm^{-1}; MS (EI) m/z 288 (M$^+$, 27), 286 (M$^+$,

79), 241 (89), 214 (51), 178 (100%); HRMS (EI) m/z 286.0767, 288.0743 (calcd for $C_{17}H_{15}ClO_2$ 286.0761, 288.0731).

Ethyl (2Z)-3-(4-nitrophenyl)-3-phenylprop-2-enoate (Xk): (2.7 mmol scale, 424 mg, purified by recrystalization, 52%); R_f = 0.4 (hexane- AcOEt = 4 : 1); yellow crystals; mp 88.5-90.0 °C (hexane-MeOH); ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 1.17 (t, J = 7.1 Hz, 3H), 4.07 (d, J = 7.1 Hz, 2H), 6.48 (s, 1H), 7.24-7.27 (m, 2H), 7.33-7.43 (m, 5H), 8.27 (d-like, J = 8.8 Hz, 2H). Selected NOEs are between δ 6.48 (C2-*H*) and δ 7.24-7.27 (2-*H* of Ph).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.12 (CH$_3$), 60.54 (CH$_2$), 118.62 (CH), 123.34 (CH), 128.08 (CH), 128.81 (CH), 130.08 (CH), 130.14 (CH), 139.24 (C), 146.13 (C), 147.57 (C), 154.50 (C), 165.49 (C). Selected HMBC correlations are between δ 6.48 (C2-*H*) and δ 139.24 (1-*C* of Ph), and δ 7.24-7.27 (2-*H* of Ph) and δ 154.50 (*C*3).; IR (KBr) 2985, 1719, 1619, 1594, 1515, 1350, 1267, 1172, 1034 cm^{-1}; MS (EI) m/z 297 (M$^+$, 80), 252 (100%); HRMS (EI) m/z 297.1010 (calcd for $C_{17}H_{15}NO_4$ 297.1001).

3,3-Bis(4-methylphenyl)prop-2-en-1-ol (Yf): (26 mmol scale, 5.915 g, 95%); colorless crystals: mp 68.5-69.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.57 (bs, 1H), 2.33 (s, 3H), 2.37 (s, 3H), 4.19 (d, J = 6.8 Hz, 2H), 6.17 (t, J = 6.8 Hz, 1H), 7.04 (d-like, J = 8.0 Hz, 2H), 7.08 (d-like, J = 8.0 Hz, 2H), 7.13-7.17 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.15 (CH$_3$), 21.29 (CH$_3$), 60.81 (CH2), 126.46 (CH), 127.62 (CH), 128.91 (CH), 129.72 (CH), 136.28 (C), 137.26 (C), 137.42 (C), 139.27 (C), 144.13 (C); IR (KBr) 3267, 2916, 1510, 1012 cm^{-1}; MS (EI) m/z 238 (M$^+$, 60), 223 (68), 195 (100%); HRMS (EI) m/z 238.1361 (calcd for $C_{17}H_{18}O$ 238.1358).

3,3-Bis(4-methoxyphenyl)prop-2-en-1-ol (Yg): (19.4 mmol scale, 5.26 g, 100%); R_f = 0.1 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.75 (bs, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 4.20 (d. J = 7.0 Hz, 2H), 6.09 (t, J = 7.0 Hz, 1H), 6.81 (d-like, J = 8.9 Hz, 2H), 6.88 (d-like, J = 8.8 Hz, 2H), 7.07 (d-like, J = 8.8 Hz, 2H), 7.18 (d-like, J = 8.9 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 55.29 (CH$_3$), 55.31 (CH$_3$), 60.81 (CH$_2$), 113.54 (CH), 113.56

(CH), 125.46 (CH), 128.92 (CH), 131.01 (CH), 131.60 (C), 134.86 (C), 143.48 (C), 159.01 (C), 159.24 (C); IR (neat) 3344, 2933, 2835, 1607, 1511, 1245, 1174, 1034 cm^{-1}; MS (EI) m/z 270 (M$^+$, 52), 242 (29), 227 (100), 135 (65%); HRMS (EI) m/z 270.1253 (calcd for $C_{17}H_{18}O_3$ 270.1256).

(2Z)-3-(2-Chlorophenyl)-3-phenylprop-2-en-1-ol (Yh): (11.4 mmol scale, 2.67 g, 96%); R_f = 0.1 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.55 (bs, 1H), 4.03-4.08 (m, 2H), 6.44 (t, J = 6.8 Hz, 1H), 7.18-7.20 (m, 1H), 7.22-7.33 (m, 7H), 7.43-7.48 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 60.99 (CH$_2$), 126.58 (CH), 126.96 (CH), 127.83 (CH), 128.46 (CH), 128.60 (CH), 129.15 (CH), 129.82 (CH), 131.50 (CH), 133.61 (C), 137.75 (C), 139.66 (C), 140.79 (C); IR (neat) 3327, 3056, 2867, 1597, 1494, 1472, 1446, 1052, 1035 cm^{-1}; MS (EI) m/z 246 (M$^+$, 11), 244 (M$^+$, 32), 209 (100%); HRMS (EI) m/z 244.0651, 246.0625 (calcd for $C_{15}H_{13}ClO$ 244.0655, 246.0625); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.43 (bs, 1H), 3.93 (bs, 2H), 6.33-6.39 (m, 1H), 6.78-6.88 (m, 2H), 6.92-6.97 (m, 1H), 7.00-7.09 (m, 3H), 7.19 (dd, J = 7.7, 1.5 Hz, 1H), 7.22-7.25 (m, 2H). Selected NOEs are between δ 6.33-6.39 (CH=CPh) and δ 7.22-7.25 (2'-H of CH=CPh) and between δ 3.93 (CH_2) and δ 6.92-6.97 (6-H of 2-chlorophenyl) in C$_6$D$_6$.; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 60.75 (CH$_2$), 126.82 (CH), 126.90 (CH), 127.76 (CH), 128.65 (CH), 129.05 (CH), 129.89 (CH), 129.91 (CH), 131.77 (CH), 134.08 (C), 138.37 (C), 140.17 (C), 140.25 (C).

(2Z)-3-(4-Chlorophenyl)-3-phenylprop-2-en-1-ol (Yi): (8.75 mmol scale, 2.37 g, 94%); R_f = 0.4 (hexane-ether = 1 : 1); colorless crystals; mp 88.5-89.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.48 (bs, 1H), 4.20 (d, J = 6.8 Hz, 2H), 6.24 (t, J = 6.8 Hz, 1H), 7.11 (d-like, J = 8.6 Hz, 2H), 7.22-7.32 (m, 5H), 7.35 (d-like, J = 8.6 Hz, 2H). Selected NOEs are between δ 4.20 (CH_2) and δ 7.11 (2-H of 4-chlorophenyl).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 60.66 (CH$_2$), 127.88 (CH), 127.91 (CH), 128.02 (CH), 128.37 (CH), 128.57 (CH), 131.21 (CH), 133.67 (C), 137.55 (C), 141.47 (C), 143.26 (C); IR (KBr) 3270, 2860, 1594, 1491, 1091, 1015 cm^{-1}; MS (EI) m/z 246 (M$^+$,

23), 244 (M$^+$, 70), 201 (100%); HRMS (EI) *m/z* 244.0647, 246.0615 (calcd for C$_{15}$H$_{13}$ClO 244.0655, 246.0625).

(2*Z*)-3-(4-Nitrophenyl)-3-phenylprop-2-en-1-ol (Yk): (5 mmol scale, 854 mg, 88%); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.12 (bs, 1H), 4.19 (d, *J* = 6.9 Hz, 2H), 6.34 (t, *J* = 6.9 Hz, 1H), 7.18-7.21 (m, 2H), 7.28-7.32 (m, 3H), 7.35 (d-like, *J* = 8.8 Hz, 2H), 8.21 (d-like, *J* = 8.8 Hz, 2H). Selected NOEs are between δ 6.34 (C*H*=CPh) and δ 7.18-7.21 (2'-*H* of CH=C*Ph*) between δ 4.19 (C*H$_2$*) and δ 7.35 (2-*H* of 4-nitrophenyl).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 60.27 (CH$_2$), 123.53 (CH), 127.56 (CH), 128.21 (CH), 128.51 (CH), 129.34 (CH), 130.75 (CH), 140.57 (C), 142.29 (C), 146.10 (C), 147.21 (C); IR (neat) 3359, 3078, 1520, 1347, 1107, 1014 cm^{-1}; MS (EI) *m/z* 255 (M$^+$, 100), 237 (79), 212 (61), 165 (78%); HRMS (EI) *m/z* 255.0892 (calcd for C$_{15}$H$_{13}$NO$_3$ 255.0895).

Preparation of Yj. A mixture of Pd(OAc)$_2$ (22 mg, 0.1 mmol), PPh$_3$ (52 mg, 0.2 mmol), 4-chlorophenylboronic acid (2.4 mmol), KOH (224 mg, 4 mmol), MeOH (8 mL), and THF (8 mL) was heated at 60 °C overnight. After cooling to room temperature, the solution was taken up in Et$_2$O (30 mL) and the Et$_2$O layer was washed with aq 1.0 M NaOH (10 mL) and brine (2 × 5 mL). The organic layer was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent. The *E*-configuration of the products was assigned by 2D-NOESY.

(2*E*)-3-(4-Chlorophenyl)-3-phenylprop-2-en-1-ol (Yj): (6.8 mmol scale, 1.49 g, 90%); R$_f$ = 0.3 (hexane-AcOEt = 1 : 1); colorless crystals; mp 72.0-73.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.53 (bs, 1H), 4.21 (d, *J* = 6.8 Hz, 2H), 6.22 (t, *J* = 6.8 Hz, 1H), 7.12-7.15 (m, 2H), 7.18 (d-like, *J* = 8.6 Hz, 2H), 7.25 (d-like, *J* = 8.6 Hz, 2H), 7.32-7.40 (m, 3H). Selected NOEs are between δ 4.21 (C*H$_2$*) and δ 7.12-7.15 (2'-*H* of CH=C*Ph*) and between δ 6.22 (C*H*=CAr) and δ 7.18 (2-*H* of 4-chlorophenyl).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 60.71 (CH$_2$), 127.88 (CH),

127.97 (CH), 128.42 (CH), 128.95 (CH), 129.73 (CH), 133.57 (C), 138.64 (C), 140.33 (C), 143.15 (C); IR (neat) 3261, 2848, 1488, 1092, 1010 cm^{-1}; MS (EI) m/z 246 (M$^+$, 22), 244 (M$^+$, 67), 226 (37), 209 (61), 201 (100%); HRMS (EI) m/z 244.0651, 246.0625 (calcd for C$_{15}$H$_{13}$ClO 244.0655, 246.0625).

3,3-Diaryl-2-propen-1-amines **4a-k** were prepared from the corresponding alcohols **Ya**, **Yc-k**. The corresponding bromides were prepared by reaction of the alcohols with PBr$_3$ in ether and used without further purification. 3,3-Diaryl-2-propen-1-amines **4a-k** were prepared by reaction of benzylamine (2 equiv) with the corresponding bromide in ether according to the literature procedure.[15]

4a: (1.5 mmol scale, 216 mg, 48%); R$_f$ = 0.1 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.00 (bs, 1H), 3.35 (d, J = 7.0 Hz, 2H), 3.75 (s, 2H), 6.22 (t, J = 7.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.19-7.36 (m, 13H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.02 (CH$_2$), 53.43 (CH$_2$), 127.05 (CH), 127.30 (CH), 127.34 (CH), 127.48 (CH), 128.19 (CH), 128.24 (CH), 128.26 (CH), 128.44 (CH), 129.81 (CH), 139.64 (C), 139.99 (C), 142.21 (C), 143.83 (C); IR (neat) 3330, 3026, 2836, 1598, 1495, 1443, 1114, 1073, 1028 cm^{-1}; MS (EI) m/z 299 (M$^+$, 70), 298 (21), 222 (30), 208 (66), 132 (49), 91 (100%); HRMS (EI) m/z 299.1678 (calcd for C$_{22}$H$_{21}$N 299.1674).

4b: (10 mmol scale, 1.31 g, 43%); R$_f$ = 0.1 (hexane-ether = 1 : 1); colorless crystals; mp 67.5-68.5 °C; 1H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.803-0.901 (m, 2H), 1.06-1.24 (m, 4H), 1.31-1.42 (m, 1H), 1.62-1.70 (m, 5H), 2.38 (d, J = 6.6 Hz, 2H), 3.27 (d, J = 6.8 Hz, 2H), 6.18 (t, J = 6.8 Hz, 1H), 7.14-7.34 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 25.93 (CH$_2$), 26.57 (CH$_2$), 31.29 (CH$_2$), 37.80 (CH), 48.60 (CH$_2$), 56.19 (CH$_2$), 126.99 (CH), 127.20 (CH), 127.94 (CH), 127.98 (CH), 128.04 (CH), 129.60 (CH), 139.61 (C), 142.06 (C), 142.96 (C); IR (neat) 3317, 3076, 2925, 2846, 1596, 1493, 1444, 1363, 1118 cm^{-1}; MS (EI) m/z 305 (M$^+$, 46), 302 (11),

222 (11), 193 (100%); HRMS (EI) m/z 305.2145 (calcd for $C_{22}H_{27}N$ 305.2143); Anal. Calcd for $C_{22}H_{27}N$: C, 86.51; H, 8.91; N, 4.59. Found: C, 86.35; H, 8.66; N, 4.49.

4c: (2 mmol scale, 501 mg, 74%); R_f = 0.4 (hexane-ether = 4 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.60 (bs, 1H), 3.32 (d, J = 6.8 Hz, 2H), 3.75 (s, 2H), 6.13 (t, J = 6.8 Hz, 1H), 6.92-6.98 (m, 2H), 7.01-7.06 (m, 2H), 7.07-7.12 (m, 2H), 7.14-7.19 (m, 2H), 7.21-7.32 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.00 (CH$_2$), 53.59 (CH$_2$), 115.10 (CH, d, J_{FC} = 21 Hz), 115.27 (CH, d, J_{FC} = 21 Hz), 127.09 (CH), 127.90 (CH), 128.19 (CH), 128.47 (CH), 129.03 (CH, d, J_{FC} = 8.4 Hz), 131.39 (CH, d, J_{FC} = 8.4 Hz), 135.28 (C, d, J_{FC} = 3.1 Hz), 138.22 (C, d, J_{FC} = 3.1 Hz), 140.06 (C), 141.63 (C), 162.13 (C, d, J_{FC} = 247 Hz), 162.32 (C, d, J_{FC} = 247 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -115.14 (m), -114.68 (m); IR (neat) 3330, 3028, 2835, 1601, 1508, 1453, 1224, 1159, 1095 cm^{-1}; MS (EI) m/z 335 (M$^+$, 94), 244 (70), 132 (67), 91 (100%); HRMS (EI) m/z 335.1482 (calcd for $C_{22}H_{19}F_2N$ 335.1486).

4d: (2.5 mmol scale, 446 mg, 48%); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.61 (bs, 1H), 3.31 (d, J = 6.8 Hz, 2H), 3.73 (s, 2H), 6.17 (t, J = 6.8 Hz, 1H), 7.05 (d-like, J = 8.7 Hz, 2H), 7.11 (d-like, J = 8.7 Hz, 2H), 7.20-7.32 (m, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.98 (CH$_2$), 53.62 (CH$_2$), 127.08 (CH), 128.15 (CH), 128.43 (CH), 128.47 (CH), 128.60 (CH), 128.69 (CH), 128.89 (CH), 131.10 (CH), 133.41 (C), 133.49 (C), 137.57 (C), 140.09 (C), 140.29 (C), 141.37 (C); IR (neat) 3028, 2837, 1591, 1492, 1091, 1014 cm^{-1}; MS (EI) m/z 369 (M$^+$, 6.5), 367 (M$^+$, 10), 278 (7.3), 276 (10), 165 (60), 164 (58), 106 (100%); HRMS (EI) m/z 367.0887, 369.0887 (calcd for $C_{22}H_{19}Cl_2N$ 367.0895, 369.0865).

4e: (1.9 mmol scale, 592 mg, 72%); R_f = 0.3 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.52 (bs, 1H), 3.34 (d, J = 6.8 Hz, 2H), 3.76 (s, 2H), 6.30 (t, J = 6.8 Hz, 1H), 7.22-7.34 (m, 7H), 7.39 (dd, J = 7.7, 7.7 Hz, 1H), 7.41 (s, 1H), 7.47-7.53 (m, 3H), 7.61 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.98 (CH$_2$), 53.75 (CH$_2$), 123.96 (CH, q, J_{FC} = 3.8 Hz), 124.08 (C, q, J_{FC} = 272 Hz), 124.12 (C, q, J_{FC} = 273 Hz), 124.37 (CH, q,

J_{FC} = 3.8 Hz), 124.64 (CH, q, J_{FC} = 3.8 Hz), 126.46 (CH, q, J_{FC} = 3.8 Hz), 127.19 (CH), 128.19 (CH), 128.53 (CH), 128.89 (CH), 129.05 (CH), 130.84 (CH), 130.92 (C, q, J_{FC} = 32 Hz), 130.96 (CH), 130.99 (C, q, J_{FC} = 32 Hz), 133.17 (CH), 139.59 (C), 140.00 (C), 141.05 (C), 142.31 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -62.62, -62.69; IR (neat) 3030, 2836, 1608, 1589, 1495, 1331, 1168, 1125, 1074 cm^{-1}; MS (EI) m/z 435 (M$^+$, 24), 344 (18), 132 (33), 91 (100%); HRMS (EI) m/z 435.1418 (calcd for C$_{24}$H$_{19}$F$_6$N 435.1422).

4f: (2 mmol scale, 234 mg, 35%); R$_f$ = 0.2 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.44 (bs, 1H), 2.31 (s, 3H), 2.37 (s, 3H), 3.35 (d, J = 6.8 Hz, 2H), 3.74 (s, 2H), 6.14 (t, J = 6.8 Hz, 1H), 7.02-7.07 (m, 4H), 7.12-7.15 (m, 4H), 7.19-7.30 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 21.13 (CH$_3$), 21.31 (CH$_3$), 48.24 (CH$_2$), 53.59 (CH$_2$), 126.73 (CH), 126.92 (CH), 127.41 (CH), 128.20 (CH), 128.40 (CH), 128.85 (CH), 129.72 (CH), 136.83 (C), 136.85 (C), 136.99 (C), 139.69 (C), 140.41 (C), 143.38 (C); IR (neat) 3316, 3024, 2919, 1512, 1453, 1111 cm^{-1}; MS (EI) m/z 327 (M$^+$, 26), 236 (27), 195 (42), 119 (69), 91 (100%); HRMS (EI) m/z 327.1985 (calcd for C$_{24}$H$_{25}$N 327.1987).

4g: (2.9 mmol scale, 365 mg, 35%); R$_f$ = 0.2 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.48 (bs, 1H), 3.35 (d, J = 7.0 Hz, 2H), 3.75 (s, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 6.07 (t, J = 7.0 Hz, 1H), 6.80 (d-like, J = 8.9 Hz, 2H), 6.87 (d-like, J = 8.8 Hz 2H), 7.07 (d-like, J = 8.8 Hz, 2H), 7.17 (d-like, J = 8.9 Hz, 2H), 7.21-7.31 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.26 (CH$_2$), 53.62 (CH$_2$), 55.31 (CH$_3$), 55.33 (CH$_3$), 113.51 (CH), 113.53 (CH), 125.76 (CH), 126.94 (CH), 128.22 (CH), 128.42 (CH), 128.68 (CH), 130.99 (CH), 132.20 (C), 135.32 (C), 140.41 (C), 142.69 (C), 158.77 (C), 159.01 (C); IR (neat) 3328, 2953, 2834, 1606, 1511, 1246, 1173, 1035 cm^{-1}; MS (EI) m/z 359 (M$^+$, 100), 268 (52%); HRMS (EI) m/z 359.1878 (calcd for C$_{24}$H$_{25}$NO$_2$ 359.1887).

4h: (3.1 mmol scale, 515 mg, 50%); R$_f$ = 0.4 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.49 (bs, 1H), 3.17-3.21 (m, 2H), 3.73 (s, 2H), 6.41 (t, J = 6.8 Hz,

1H), 7.14-7.16 (m, 1H), 7.17-7.29 (m, 12H), 7.41-7.44 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.27 (CH$_2$), 53.59 (CH$_2$), 126.35 (CH), 126.78 (CH), 126.91 (CH), 127.40 (CH), 128.08 (CH), 128.34 (CH), 128.37 (CH), 128.82 (CH), 129.00 (CH), 129.72 (CH), 131.49 (CH), 133.73 (C), 138.22 (C), 139.99 (C), 140.25 (C), 140.35 (C); IR (neat) 3026, 2835, 1597, 1495, 1445, 1362, 1125, 1050 cm^{-1}; MS (EI) m/z 335 (M$^+$, 7.5), 333 (M$^+$, 18), 298 (42), 91 (100%); HRMS (EI) m/z 333.1282, 335.1245 (calcd for C$_{22}$H$_{20}$ClN 333.1284, 335.1255).

4i: (3.5 mmol scale, 531 mg, 45%); R$_f$ = 0.5 (hexane-AcOEt = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.59 (bs, 1H), 3.33 (d, J = 6.8 Hz, 2H), 3.75 (s, 2H), 6.21 (t, J = 6.8 Hz, 1H), 7.08 (d-like, J = 8.4 Hz, 2H), 7.19-7.33 (m, 12H). Selected NOEs are between δ 3.33 (CH_2-CH=) and δ 7.08 (2'-H of 4-chlorophenyl).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.01 (CH$_2$), 53.59 (CH$_2$), 127.09 (CH), 127.47 (CH), 127.55 (CH), 128.21 (CH), 128.31 (CH), 128.49 (CH), 131.21 (CH), 133.25 (C), 138.08 (C), 140.14 (C), 141.82 (C), 142.55 (C); IR (neat) 3316, 3027, 2833, 1597, 1489, 1445, 1090, 1015 cm^{-1}; MS (EI) m/z 335 (M$^+$, 16), 333 (M$^+$, 16), 242 (41), 132 (49), 91 (100%); HRMS (EI) m/z 333.1277, 335.1266 (calcd for C$_{22}$H$_{20}$ClN 333.1284, 335.1255).

4j: (2.4 mmol scale, 805 mg, 41%); R$_f$ = 0.3 (hexane-AcOEt = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.50 (bs, 1H), 3.34 (d, J = 6.8 Hz, 2H), 3.74 (s, 2H), 6.18 (t, J = 6.8 Hz, 1H), 7.11-7.16 (m, 4H), 7.20-7.37 (m, 10H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.14 (CH$_2$), 53.63 (CH$_2$), 127.02 (CH), 127.51 (CH), 128.18 (CH), 128.32 (CH), 128.34 (CH), 128.45 (CH), 128.73 (CH), 129.74 (CH), 133.15 (C), 139.18 (C), 140.24 (C), 140.73 (C), 142.46 (C); IR (neat) 3323, 3027, 2836, 1599, 1488, 1453, 1442, 1092, 1012 cm^{-1}; MS (EI) m/z 335 (M$^+$, 23), 333 (M$^+$, 65), 242 (55), 132 (69), 91 (100%); HRMS (EI) m/z 333.1279, 335.1266 (calcd for C$_{22}$H$_{20}$ClN 333.1284, 335.1255).

4k: (2.6 mmol scale, 432 mg, 48%); R$_f$ = 0.2 (hexane-AcOEt = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.54 (bs, 1H), 3.31 (d, J = 7.0 Hz, 2H), 3.76 (s, 2H), 6.30 (t, J = 7.0

Hz, 1H), 7.16-7.18 (m, 2H), 7.23-7.32 (m, 10H), 8.18 (d-like, J = 8.8 Hz, 2H). Selected NOEs are between δ 6.30 (C*H*=CPh) and δ 7.16-7.18 (2-*H* of CH=C*Ph*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 47.78 (CH$_2$), 53.53 (CH$_2$), 123.48 (CH), 127.12 (CH), 127.41 (CH), 127.88 (CH), 128.13 (CH), 128.45 (CH), 129.69 (CH), 130.72 (CH), 139.88 (C), 140.94 (C), 141.75 (C), 146.64 (C), 147.02 (C); IR (neat) 3026, 2838, 1598, 1516, 1346, 1107 cm^{-1}; MS (EI) *m/z* 344 (M$^+$, 31), 253 (22), 132 (35), 91 (100%); HRMS (EI) *m/z* 344.1521 (calcd for C$_{22}$H$_{20}$N$_2$O$_2$ 344.1525).

Typical experimental procedure for 5 (Table 4-2, entry 2). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (136 mg, 0.5 mmol) upon treatment with CF$_3$CO$_2$H (2 mL))[17] in DMF (0.7 mL) were added *N*-benzyl 3,3-diphenyl-2-propen-1-amine (**4a**) (150 mg, 0.5 mmol) in DMF (0.7 mL), Et$_3$N (0.07 mL, 51 mg, 0.5 mmol), HOBt (1-hydroxybenzotriazole) (135 mg, 1 mmol), and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (100 mg, 0.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **5a-*trans*** (129 mg, 52%).

5a-*trans*: R$_f$ = 0.4 (hexane-ether = 1 : 4); colorless crystals; mp 159.5-160 °C (hexane-AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.60 (dd, J = 9.6, 9.0 Hz, 1H), 2.96 (dddd, J = 13.5, 9.6, 8.0, 6.3 Hz, 1H), 3.24 (dd, J = 9.0, 8.0 Hz, 1H), 3.48 (d, J = 13.5 Hz, 1H), 3.78 (d, J = 15.0 Hz, 1H), 4.16 (qd, J = 10.8, 7.1 Hz, 1H), 4.29-4.48 (m, 4H), 4.90 (d, J = 15.0 Hz, 1H), 6.90 (d, J = 6.8 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 7.18-7.32 (m, 10H), 7.53 (dd, J = 8.0, 1.0 Hz, 1H). Selected NOEs are between δ 2.96 (C3a-*H*) and δ 3.24 (C3-H*H*),

and between δ 2.60 (C3-*H*H) and δ 3.48 (C9a-*H*), and between δ 2.60 (C3-*H*H) and δ 6.90 (*o*-H of C4-*Ph*). Atom numbering is shown in Table 4-3.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.00 (CH$_3$), 14.13 (CH$_3$), 36.37 (CH), 43.81 (CH), 46.15 (CH$_2$), 46.91 (CH), 47.32 (CH$_2$), 60.32 (C), 62.03 (CH$_2$), 62.51 (CH$_2$), 126.99 (CH), 127.01 (CH), 127.39 (CH), 127.92 (CH), 128.41 (CH), 128.50 (CH), 128.61 (CH), 130.25 (CH), 130.52 (CH), 131.45 (CH), 134.64 (CH), 136.80 (C), 138.80 (C), 141.18 (C), 168.44 (C), 170.96 (C), 171.86 (C). Selected HMBC correlations are between δ 2.96 (C9a-*H*) and δ 36.37 (*C*3a), between δ 2.60 (C3-*H*H), 2.96 (C3a-*H*), 6.98 (C5-*H*) and δ 46.91 (*C*4), and between δ 2.96 (C3a-*H*), 3.48 (C9a-*H*) and δ 60.32 (*C*9).; IR (KBr) 2977, 1735, 1691, 1496, 1441, 1249, 1025 cm^{-1}; MS (EI) *m/z* 497 (M$^+$, 75), 394 (45), 91 (100%); HRMS (EI) *m/z* 497.2201 (calcd for C$_{31}$H$_{31}$NO$_5$ 497.2202).

5a-*cis*: (1 mmol scale, benzene, 80 °C, 247 mg, 48%); R$_f$ = 0.2 (hexane-ether = 1 : 8); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.15 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 3.00 (dd, *J* = 9.6, 7.4 Hz, 1H), 3.14 (dd, *J* = 9.6, 8.2 Hz, 1H), 3.35 (dddd, *J* = 10.0, 8.2, 7.4, 5.1 Hz, 1H), 4.03-4.09 (m, 1H), 4.10 (d, *J* = 15.2 Hz, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 4.18-4.27 (m, 1H), 4.29 (d, *J* = 5.1 Hz, 1H), 4.31 (d, *J* = 15.2 Hz, 1H), 4.33-4.46 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.93-6.95 (m, 2H), 7.06-7.08 (m, 2H), 7.13-7.33 (m, 8H), 8.09 (dd, *J* = 8.0, 1.0 Hz, 1H). Selected NOEs are between δ 3.35 (C3a-*H*) and δ 4.20 (C9a-*H*), 4.29 (C4-*H*) (overlapped), and between δ 4.29 (C4-*H*) and δ 6.87 (C5-*H*), 7.06-7.08 (*o*-H of C4-*Ph*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.80 (CH$_3$), 14.05 (CH$_3$), 36.38 (CH), 45.08 (CH), 46.40 (CH$_2$), 47.58 (CH), 48.49 (CH$_2$), 59.24 (C), 61.94 (CH$_2$), 62.39 (CH$_2$), 126.66 (CH), 127.19 (CH), 127.31 (CH), 127.57 (CH), 127.76 (CH), 128.58 (CH), 128.66 (CH), 129.84 (CH), 130.94 (CH), 132.54 (C), 135.93 (C), 138.18 (C), 139.90 (C), 168.70 (C), 169.71 (C), 172.70 (C). Selected HMBC correlations are between δ 3.00 (C3-*H*H), 3.52 (C3-H*H*), 4.20 (C9a-*H*), 4.29 (C4-*H*) and δ 36.38 (*C*3a), between δ 3.00 (C3-*H*H), 3.52 (C3-H*H*), 3.35 (C3a-*H*), 7.06-7.08 (*o*-H of C4-*Ph*) and δ 45.08 (*C*4), and between δ 4.20 (C9a-*H*) and δ 59.24 (*C*9).; IR (KBr) 2980, 1729, 1694, 1495,

1445, 1239, 1029 cm^{-1}; MS (EI) m/z 497 (M$^+$, 46), 423 (6.4), 350 (13), 276 (22), 91 (100%); HRMS (EI) m/z 497.2195 (calcd for C$_{31}$H$_{31}$NO$_5$ 497.2202).

5b-*cis*: (1 mmol scale, benzene, 80 °C, 277 mg, 55%); R_f = 0.2 (hexane-ether = 1 : 1); pale yellow crystals; mp 47.5-48.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.669-0.825 (m, 2H), 0.959-1.11 (m, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.22-1.26 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.36-1.43 (m, 2H), 1.51-1.61 (m, 3H), 2.72 (dd, J = 13.6, 7.3 Hz, 1H), 2.95 (dd, J = 13.6, 7.5 Hz, 1H), 3.05 (dd, J = 9.3, 7.5 Hz, 1H), 3.26 (dd, J = 9.3, 8.2 Hz, 1H), 3.36 (dddd, J = 9.6, 8.2, 7.5, 4.9 Hz, 1H), 4.01-4.09 (m, 1H), 4.12 (d, J = 9.6 Hz, 1H), 4.18-4.26 (m, 1H), 4.31 (d, J = 4.9 Hz, 1H), 4.31-4.43 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 7.15-7.18 (m, 3H), 7.24-7.33 (m, 2H), 7.36-7.40 (m, 2H), 8.04 (dd, J = 8.0, 1.2 Hz, 1H). Selected NOEs are between δ 3.36 (C3a-*H*) and δ 4.12 (C9a-*H*), 4.31 (C4-*H*), and between δ 4.31 (C4-*H*) and δ 6.92 (C5-*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.80 (CH$_3$), 14.05 (CH$_3$), 25.75 (CH$_2$), 26.38 (CH$_2$), 30.34 (CH$_2$), 30.61 (CH$_2$), 35.55 (CH), 36.45 (CH), 45.09 (CH), 47.73 (CH), 48.92 (CH2), 49.83 (CH2), 59.13 (C), 61.81 (CH2), 62.35 (CH2), 126.64 (CH), 127.23 (CH), 127.48 (CH), 127.67 (CH), 128.73 (CH), 129.86 (CH), 130.97 (CH), 132.66 (C), 138.20 (C), 140.11 (C), 168.56 (C), 169.81 (C), 172.60 (C). Selected HMBC correlations are between δ 3.05 (C3-*H*H), 3.26 (C3-H*H*), 4.12 (C9a-*H*), 4.31 (C4-*H*) and δ 36.45 (*C*3a), between δ 3.05 (C3-*H*H), 6.92 (C5-*H*) and δ 45.09 (*C*4), and between δ 4.12 (C9a-*H*) and δ 59.13 (*C*9).; IR (KBr) 2924, 1730, 1695, 1448, 1238, 1038 cm^{-1}; MS (EI) m/z 503 (M$^+$, 5.3), 205 (6.9), 86 (100%); HRMS (EI) m/z 503.2672 (calcd for C$_{31}$H$_{37}$NO$_5$ 503.2672).

5c-*trans*: (0.5 mmol scale, DMF, r.t., 141 mg, 53%); R_f = 0.2 (hexane-ether = 1 : 8); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 2.58 (dd, J = 9.7, 9.1 Hz, 1H), 2.94 (dddd, J = 13.5, 9.7, 7.7, 6.1 Hz, 1H), 3.24 (dd, J = 9.1, 7.7 Hz, 1H), 3.37 (d, J = 13.5 Hz, 1H), 3.83 (d, J = 15.0 Hz, 1H), 4.17 (dq, J = 10.7, 7.1 Hz, 1H), 4.30-4.50 (m, 4H), 4.88 (d, J = 15.0 Hz, 1H), 6.86 (dd, J = 8.6, 5.3 Hz, 2H), 6.93-7.00 (m, 4H),

7.21-7.32 (m, 6H). Selected NOEs are between δ 2.94 (C3a-*H*) and δ 3.24 (C3-H*H*) and between δ 2.58 (C3-*H*H) and δ 3.37 (C9a-*H*), and between δ 2.58 (C3-*H*H) and δ 6.86 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.98 (CH$_3$), 14.12 (CH$_3$), 36.42 (CH), 43.48 (CH), 45.57 (CH), 46.17 (CH$_2$), 47.13 (CH$_2$), 60.14 (C), 62.29 (CH$_2$), 62.85 (CH$_2$), 115.54 (CH, d, J_{FC} = 21 Hz), 116.28 (CH, d, J_{FC} = 21 Hz), 116.92 (CH, d, J_{FC} = 23 Hz), 127.50 (CH), 127.91 (CH), 128.66 (CH), 131.54 (CH, d, J_{FC} = 8.4 Hz), 132.74 (CH, d, J_{FC} = 7.7 Hz), 134.47 (C, d, J_{FC} = 3.1 Hz), 136.43 (C, d, J_{FC} = 7.7 Hz), 136.55 (C), 136.57 (C), 161.25 (C, d, J_{FC} = 246 Hz), 161.85 (C, d, J$_{FC}$ = 247 Hz), 167.79 (C), 170.48 (C), 171.38 (C). Selected HMBC correlations are between δ 2.58 (C3-*H*H), 3.24 (C3-H*H*) and δ 36.42 (*C*3a), between δ 6.86 (*o*-H of C4-*Ph*) and δ 45.57 (*C*4), and between δ 2.94 (C3a-*H*), 3.37 (C9a-*H*) and δ 60.14 (*C*9).; ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -114.56 (ddd, J = 10.3, 6.9, 6.9 Hz), -115.29 (m); IR (KBr) 2979, 1735, 1691, 1507, 1495, 1260, 1161, 1028 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 18), 430 (12), 57 (100%); HRMS (EI) *m/z* 533.2013 (calcd for C$_{31}$H$_{29}$F$_2$NO$_5$ 533.2014).

5c-*cis*: (0.54 mmol scale, toluene, 110 °C, 282 mg, 98%); R$_f$ = 0.5 (hexane-ether = 1 : 4); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.17 (t, J = 7.0 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 2.93 (dd, J = 9.6, 7.0 Hz, 1H), 3.13 (dd, J = 9.6, 8.3 Hz, 1H), 3.33 (dddd, J = 9.8, 8.3, 7.0, 5.1 Hz, 1H), 4.03-4.11 (m, 1H), 4.18-4.28 (m, 5H), 4.34-4.50 (m, 2H), 6.79 (dd, J = 8.5, 6.0 Hz, 1H), 6.88 (ddd, J = 8.5, 8.2, 2.7 Hz, 1H), 6.92-6.94 (m, 2H), 7.00-7.02 (m, 4H), 7.19-7.22 (m, 3H), 8.01 (dd, J_{FH} = 11.0, J_{HH} = 2.7 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.80 (CH$_3$), 14.05 (CH$_3$), 36.13 (CH), 43.78 (CH), 46.36 (CH$_2$), 47.36 (CH), 48.08 (CH$_2$), 58.77 (C), 62.18 (CH$_2$), 62.67 (CH$_2$), 114.79 (CH, d, J_{FC} = 21 Hz), 115.66 (CH, d, J_{FC} = 21 Hz), 118.07 (CH, d, J_{FC} = 25 Hz), 127.49 (CH), 127.56 (CH), 128.65 (CH), 128.69 (CH, d, J_{FC} = 9.2 Hz), 131.27 (CH, d, J_{FC} = 8.4 Hz), 133.71 (C, d, J_{FC} = 3.1 Hz), 134.29 (C, d, J_{FC} = 8.4 Hz), 135.14 (C, d, J_{FC} = 3.1 Hz), 135.62 (C), 161.52 (C, d, J_{FC} = 245 Hz), 161.92 (C, d, J_{FC} = 246 Hz), 168.15 (C), 168.95 (C), 172.25 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -115.06 ~ -114.93 (m, 2F); ^{1}H

NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.787 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.62 (dd, J = 9.4, 8.4 Hz, 1H), 2.69 (dd, J = 9.4, 7.0 Hz, 1H), 2.85 (dddd, J = 9.6, 8.4, 7.0, 4.9 Hz, 1H), 3.70 (dq, J = 10.7, 7.0 Hz, 1H), 3.94 (d, J = 15.0 Hz, 1H), 4.02 (dq, J = 10.7, 7.0 Hz, 1H), 4.14 (d, J = 15.0 Hz, 1H), 4.21 (d, J = 4.9 Hz, 1H), 4.38 (d, J = 9.6 Hz, 1H), 4.38-4.51 (m, 2H), 6.56-6.60 (m, 3H), 6.65-6.70 (m, 3H), 6.88-6.96 (m, 3H), 7.01-7.05 (m, 2H), 8.54 (dd, J_{FH} = 11.1, J_{HH} = 2.7 Hz, 1H). Selected NOEs are between δ 2.85 (C3a-H) and δ 4.38 (C9a-H), 4.21 (C4-H), and between δ 4.21 (C4-H) and δ 4.38 (C9a-H).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 13.57 (CH$_3$), 13.98 (CH$_3$), 36.44 (CH), 44.09 (CH), 46.37 (CH$_2$), 47.54 (CH), 47.85 (CH$_2$), 59.30 (C), 62.36 (CH$_2$), 62.47 (CH$_2$), 114.86 (CH, d, J_{FC} = 21 Hz), 115.61 (CH, d, J_{FC} = 21 Hz), 118.68 (CH, d, J_{FC} = 25 Hz), 127.59 (CH), 127.72 (CH), 128.78 (CH), 129.04 (CH, d, J_{FC} = 7.7 Hz), 131.45 (CH, d, J_{FC} = 7.7 Hz), 134.45 (C, d, J_{FC} = 3.1 Hz), 135.30 (C, d, J_{FC} = 8.4 Hz), 135.58 (C, d, J_{FC} = 3.1 Hz), 136.41 (C), 161.97 (C, d, J_{FC} = 244 Hz), 162.14 (C, d, J_{FC} = 245 Hz), 168.29 (C), 169.31 (C), 171.83 (C). Selected HMBC correlations are between δ 2.69 (C3-HH), 4.38 (C9a-H), 4.21 (C4-H) and δ 36.44 (C3a), between δ 2.69 (C3-HH) and δ 44.09 (C4), and between δ 2.85 (C3a-H), 4.38 (C9a-H), 8.54 (C8-H) and δ 59.30 (C9).; ^{19}F NMR (376 MHz, C$_6$D$_6$) δ (ppm) -114.89 (m, 1F), -115.20 (m, 1F); IR (neat) 2982, 1732, 1699, 1604, 1511, 1445, 1161, 1039 cm^{-1}; MS (EI) m/z 533 (M$^+$, 52), 312 (29), 267 (25), 253 (23), 91 (100%); HRMS (EI) m/z 533.2019 (calcd for C$_{31}$H$_{29}$NO$_5$ 533.2014).

5d-*trans*: (1 mmol scale, DMF, r.t., 526 mg, 93%); R$_f$ = 0.6 (hexane-ether = 1 : 4); colorless crystals; mp 130-131 °C (hexane-AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 2.58 (dd, J = 9.7, 9.1 Hz, 1H), 2.93 (dddd, J = 13.5, 9.7, 7.7, 6.1 Hz, 1H), 3.24 (dd, J = 9.1, 7.7 Hz, 1H), 3.34 (d, J = 13.5 Hz, 1H), 3.80 (d, J = 14.9 Hz, 1H), 4.14-4.22 (m, 1H), 4.29-4.50 (m, 3H), 4.33 (d, J = 6.1 Hz, 1H), 4.89 (d, J = 14.9 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 2.1 Hz, 1H), 7.22-7.32 (m, 7H), 7.52 (d, J = 2.1 Hz, 1H). Selected NOEs are between δ 2.93 (C3a-H) and δ 3.24 (C3-HH), 4.33 (C4-H)

and between δ 2.58 (C3-*H*H) and δ 3.34 (C9a-*H*), 6.83 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.95 (CH₃), 14.09 (CH₃), 36.21 (CH), 43.56 (CH), 45.90 (CH), 46.21 (CH₂), 47.07 (CH₂), 60.06 (C), 62.29 (CH2), 62.86 (CH₂), 127.51 (CH), 127.92 (CH), 128.66 (CH), 128.83 (CH), 128.91 (CH), 130.49 (CH), 131.39 (CH), 132.46 (CH), 132.94 (C), 133.28 (C), 136.32 (C), 136.58 (C), 136.90 (C), 139.07 (C), 167.73 (C), 170.33 (C), 171.17 (C). Selected HMBC correlations are between δ 2.58 (C3-*H*H), 3.24 (C3-H*H*), 3.34 (C9a-*H*) and δ 36.21 (*C*3a), between δ 6.83 (*o*-H of C4-*Ph*) and δ 45.90 (*C*4), and between δ 2.93 (C3a-*H*), 3.34 (C9a-*H*) and δ 60.06 (*C*9).; IR (KBr) 2979, 1734, 1686, 1596, 1488, 1442, 1364, 1253, 1186, 1013 cm^{-1}; MS (EI) *m/z* 567 (M$^+$, 50), 565 (72), 464 (26), 462 (31), 91 (100%); HRMS (EI) *m/z* 565.1407, 567.1392 (calcd for C₃₁H₂₉Cl₂NO₅ 565.1423, 567.1393).

5e-*trans*: (1.02 mmol scale, THF, r.t., 644 mg, 99%); R$_f$ = 0.6 (hexane-ether = 1 : 4); colorless crystals; mp 134-135 °C; 1H NMR (400 MHz, CDCl₃) δ (ppm) 1.26 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.53 (dd, *J* = 9.7, 9.2 Hz, 1H), 3.01 (dddd, *J* = 13.7, 9.7, 7.8, 5.9 Hz, 1H), 3.31 (dd, *J* = 9.2, 7.8 Hz, 1H), 3.37 (d, *J* = 13.7 Hz, 1H), 3.84 (d, *J* = 15.0 Hz, 1H), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.30-4.48 (m, 3H), 4.51 (d, *J* = 5.9 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.18-7.32 (m, 7H), 7.43 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.53-7.58 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H). Selected NOEs are between δ 3.01 (C3a-*H*) and δ 3.31 (C3-H*H*), 4.51 (C4-*H*) and between δ 2.53 (C3-*H*H) and δ 3.37 (C9a-*H*), 7.05 (6-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.95 (CH₃), 14.00 (CH₃), 36.17 (CH), 43.37 (CH), 46.20 (CH₂), 46.84 (CH), 46.89 (CH₂), 60.24 (C), 62.50 (CH₂), 62.95 (CH₂), 123.63 (C, q, J_{FC} = 272 Hz), 123.85 (C, q, J_{FC} = 273 Hz), 124.12 (CH, q, J_{FC} = 3.1 Hz), 124.46 (CH, q, J_{FC} = 3.8 Hz), 126.59 (CH, q, J_{FC} = 3.8 Hz), 127.57 (CH), 127.93 (CH), 128.08 (CH, q, J_{FC} = 3.8 Hz), 128.68 (CH), 129.46 (CH), 130.89 (C, q, J_{FC} = 33 Hz), 131.12 (C, q, J_{FC} = 33 Hz), 131.61 (CH), 133.46 (CH), 136.41 (C), 138.46 (C), 138.77 (C), 141.07 (C), 167.53 (C), 170.05 (C), 170.97 (C). Selected HMBC correlations are between δ 2.53 (C3-*H*H), 3.31 (C3-H*H*) and δ 36.17 (*C*3a), between δ 7.05 (6-H of C4-*Ar*) and δ 46.84 (*C*4), and

between δ 3.01 (C3a-*H*), 3.37 (C9a-*H*), 7.71 (C8-*H*) and δ 60.24 (*C*9).; ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -62.70, -62.89; IR (KBr) 3062, 2984, 1739, 1704, 1620, 1607, 1415, 1330, 1253, 1166, 1132 cm^{-1}; MS (EI) *m/z* 633 (M$^+$, 84), 530 (29), 149 (14), 118 (16), 91 (100%); HRMS (EI) *m/z* 633.1951 (calcd for C$_{33}$H$_{29}$F$_6$NO$_5$ 633.1950); Anal. Calcd for C$_{33}$H$_{29}$F$_6$NO$_5$: C, 62.56; H, 4.61; N, 2.21. Found: C, 62.60; H, 4.66; N, 2.21.

5f-*cis*: (1 mmol scale, DMF, 110 °C, 292 mg, 55%); R$_f$ = 0.7 (hexane-ether = 1 : 4); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.16 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 3.00 (d, *J* = 9.6, 7.6 Hz, 1H), 3.12 (dd, *J* = 9.6, 8.3 Hz, 1H), 3.30 (dddd, *J* = 9.8, 8.3, 7.6, 5.1 Hz, 1H), 4.06 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.11 (d, *J* = 15.2 Hz, 1H), 4.18 (d, *J* = 9.8 Hz, 1H), 4.22 (d, *J* = 5.1 Hz, 1H), 4.25 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 4.35-4.46 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.92-6.97 (m, 5H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.16-7.19 (m, 3H), 7.94 (d, *J* = 1.0 Hz, 1H). Selected NOEs are between δ 3.30 (C3a-*H*) and δ 4.18 (C9a-*H*), 4.22 (C4-*H*), 3.12 (C3-H*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.78 (CH$_3$), 14.04 (CH$_3$), 21.02 (CH$_3$), 21.42 (CH$_3$), 36.36 (CH), 44.19 (CH), 46.29 (CH$_2$), 47.68 (CH), 48.40 (CH$_2$), 59.12 (C), 61.82 (CH$_2$), 62.32 (CH$_2$), 127.26 (CH), 127.33 (CH), 127.51 (CH), 128.47 (CH), 128.50 (CH), 129.26 (CH), 129.62 (CH), 131.21 (CH), 132.18 (C), 135.23 (C), 135.88 (C), 136.06 (C), 136.68 (C), 136.81 (C), 168.74 (C), 169.65 (C), 172.83 (C). Selected HMBC correlations are between δ 3.00 (C3-*H*H), 3.12 (C3-H*H*), 4.18 (C9a-*H*) and δ 36.36 (*C*3a), between δ 6.78 (C5-*H*) and δ 44.19 (*C*4), and between δ 4.18 (C9a-*H*), 7.94 (C8-*H*) and δ 59.12 (*C*9).; IR (KBr) 2980, 1730, 1696, 1495, 1444, 1237, 1041 cm^{-1}; MS (EI) *m/z* 525 (M$^+$, 15), 304 (13), 84 (100%); HRMS (EI) *m/z* 525.2523 (calcd for C$_{33}$H$_{35}$NO$_5$ 525.2515).

5h-*trans*: (0.73 mmol scale, DMF, r.t., 126 mg, 33%); R$_f$ = 0.6 (hexane-AcOEt = 1 : 1); colorless crystals; mp 183.0-183.9 °C; 1H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.25 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 2.58 (dd, *J* = 9.9, 9.4 Hz, 1H), 3.03 (dddd, *J* = 13.5, 9.9, 7.8, 6.1 Hz, 1H), 3.43 (d, *J* = 13.5 Hz, 1H), 3.48 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.79 (d, *J* = 15.2 Hz, 1H), 4.17 (dq, *J* = 10.7,

7.1 Hz, 1H), 4.29-4.49 (m, 3H), 4.91 (d, J = 15.2 Hz, 1H), 4.96 (d, J = 6.1 Hz, 1H), 6.69 (dd, J = 7.4, 2.0 Hz, 1H), 6.91 (dd, J = 7.8, 1.2 Hz, 1H), 7.11-7.33 (m, 9H), 7.39 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (dd, J = 8.0, 1.2 Hz, 1H). Selected NOEs are between δ 3.03 (C3a-*H*) and δ 3.48 (C3-H*H*), 4.96 (C4-*H*) and between δ 3.43 (C9a-*H*) and δ 2.58 (C3-*H*H), 6.69 (6-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.02 (CH$_3$), 14.15 (CH$_3$), 36.20 (CH), 43.13 (CH), 43.83 (CH), 46.11 (CH$_2$), 47.53 (CH$_2$), 60.25 (C), 62.10 (CH$_2$), 62.59 (CH$_2$), 127.22 (CH), 127.31 (CH), 127.41 (CH), 127.89 (CH), 128.29 (CH), 128.57 (CH), 128.63 (CH), 129.23 (CH), 130.60 (CH), 131.42 (CH), 132.74 (CH), 134.85 (C), 134.99 (C), 136.82 (C), 138.47 (C), 139.00 (C), 168.30 (C), 171.02 (C), 171.67 (C). Selected HMBC correlations are between δ 2.58 (C3-*H*H), 3.48 (C3-H*H*), 3.43 (C9a-*H*), 4.96 (C4-*H*) and δ 36.20 (*C*3a), between δ 6.69 (6-H of C4-*Ar*) and δ 43.13 (*C*4), and between δ 3.43 (C9a-*H*), 7.53 (C8-*H*) and δ 60.25 (*C*9).; IR (KBr) 2976, 1747, 1724, 1702, 1433, 1250, 1044 cm^{-1}; MS (EI) m/z 533 (M$^+$, 9.4), 531 (M$^+$, 24), 428 (24), 202 (21), 91 (100%); HRMS (EI) m/z 531.1807, 533.1794 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813, 533.1783).

5h-*cis*: (1 mmol scale, toluene, 110 °C, 445 mg, 84% (**5h-*cis***:**5h-*trans***=56:28), **5h-*cis*** was partially isolated by removal of 5h-*trans* by crystallization of the mixture and the subsequent column chromatography of the filtrate. 116 mg, 22%); Rf = 0.7 (hexane-AcOEt = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.18 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.89 (dd, J = 9.8, 6.4 Hz, 1H), 3.24 (dd, J = 9.8, 7.9 Hz, 1H), 3.43 (dddd, J = 9.6, 7.9, 6.4, 6.1 Hz, 1H), 3.94 (d, J = 15.0 Hz, 1H), 4.10-4.18 (m, 1H), 4.16 (d, J = 9.6 Hz, 1H), 4.20-4.28 (m, 1H), 4.32-4.45 (m, 2H), 4.33 (d, J = 15.0 Hz, 1H), 4.93 (d, J = 6.1 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.85 (dd, J = 7.8, 1.8 Hz, 1H), 6.90-6.93 (m, 2H), 7.12-7.21 (m, 6H), 7.30-7.34 (m, 1H), 7.42 (dd, J = 7.8, 1.6 Hz, 1H), 8.11 (dd, J = 8.0, 1.2 Hz, 1H). Selected NOEs are between δ 3.43 (C3a-*H*) and δ 4.16 (C9a-*H*), 4.93 (C4-*H*), 3.24 (C3-H*H*) and between δ 4.16 (C9a-*H*) and δ 4.93 (C4-*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.89 (CH$_3$), 14.05 (CH$_3$), 34.38 (CH), 40.88 (CH), 46.36 (CH$_2$), 47.62 (CH), 48.59 (CH$_2$), 58.96 (C), 61.94 (CH$_2$), 62.54 (CH$_2$), 126.75 (CH),

126.80 (CH), 127.33 (CH), 127.60 (CH), 127.80 (CH), 127.92 (CH), 128.28 (CH), 128.59 (CH), 129.88 (CH), 130.48 (CH), 130.75 (CH), 132.62 (C), 135.13 (C), 135.87 (C), 137.31 (C), 138.35 (C), 168.64 (C), 169.82 (C), 172.36 (C). Selected HMBC correlations are between δ 2.89 (C3-*H*H), 3.24 (C3-H*H*), 4.16 (C9a-*H*), 4.93 (C4-*H*) and δ 34.38 (*C*3a), between δ 6.75 (C5-*H*) and δ 40.88 (*C*4), and between δ 4.16 (C9a-*H*), 8.11 (C8-*H*) and δ 58.96 (*C*9).; IR (neat) 2981, 1730, 1697, 1443, 1237, 1039 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 22), 531 (M$^+$, 56), 384 (28), 91 (100%); HRMS (EI) *m/z* 531.1805, 533.1780 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813, 533.1783);

5i-*trans*: (0.80 mmol scale, DMF, r.t., 306 mg, 72%); R$_f$ = 0.6 (ether); colorless crystals; mp 154-156 °C (hexane-AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.25 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 2.59 (dd, *J* = 9.7, 9.1 Hz, 1H), 2.96 (dddd, *J* = 13.7, 9.7, 7.7, 6.1 Hz, 1H), 3.24 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.38 (d, *J* = 13.7 Hz, 1H), 3.82 (d, *J* = 15.0 Hz, 1H), 4.15 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.28-4.48 (m, 4H), 4.89 (d, *J* = 15.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.19-7.32 (m, 9H), 7.53 (dd, *J* = 7.9, 1.3 Hz, 1H). Selected NOEs are between δ 2.96 (C3a-*H*) and δ 3.24 (C3-H*H*), between δ 3.38 (C9a-*H*) and δ 2.59 (C3-*H*H), 6.84 (*o*-H of C4-*Ar*), and between δ 2.59 (C3-*H*H) and δ 6.84 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.99 (CH$_3$), 14.13 (CH$_3$), 36.19 (CH), 43.79 (CH), 46.19 (CH$_2$), 46.31 (CH), 47.20 (CH$_2$), 60.21 (C), 62.10 (CH$_2$), 62.60 (CH$_2$), 127.25 (CH), 127.47 (CH), 127.94 (CH), 128.54 (CH), 128.66 (CH), 128.71 (CH), 130.65 (CH), 131.31 (CH), 131.50 (CH), 133.02 (C), 134.60 (C), 136.66 (C), 138.30 (C), 139.66 (C), 168.30 (C), 170.91 (C), 171.64 (C). Selected HMBC correlations are between δ 2.59 (C3-*H*H), 3.24 (C3-H*H*), 3.38 (C9a-*H*) and δ 36.19 (*C*3a), between δ 6.84 (*o*-H of C4-*Ar*) and δ 46.31 (*C*4), and between δ 3.38 (C9a-*H*), 7.53 (C8-*H*), 2.96 (C3a-*H*) and δ 60.21 (*C*9).; IR (KBr) 2979, 1735, 1693, 1490, 1256 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 15), 531 (M$^+$, 39), 428 (21), 91 (100%); HRMS (EI) *m/z* 531.1803, 533.1790 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813, 533.1783).

5i-*cis*: (0.80 mmol scale, toluene, 110 °C, 166 mg, 39%); R_f = 0.6 (ether); colorless crystals; mp 157-159 °C (hexane-AcOEt); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.15 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.95 (dd, J = 9.6, 7.4 Hz, 1H), 3.11 (dd, J = 9.6, 8.2 Hz, 1H), 3.31 (dddd, J = 9.6, 8.2, 7.4, 5.1 Hz, 1H), 4.06 (dq, J = 10.7, 7.1 Hz, 1H), 4.11 (d, J = 14.9 Hz, 1H), 4.17 (d, J = 9.6 Hz, 1H), 4.23 (dq, J = 10.7, 7.1 Hz, 1H), 4.27 (d, J = 5.1 Hz, 1H), 4.31 (d, J = 14.9 Hz, 1H), 4.33-4.47 (m, 2H), 6.83 (d, J = 7.8 Hz, 1H), 6.93-6.95 (m, 2H), 7.00 (d-like, J = 8.4 Hz, 2H), 7.15-7.21 (m, 4H), 7.25-7.34 (m, 3H), 8.09 (dd, J = 8.1, 1.1 Hz, 1H). Selected NOEs are between δ 3.11 (C3a-*H*) and δ 4.17 (C9a-*H*), 4.27 (C4-*H*), 3.11 (C3-H*H*) and between δ 4.17 (C9a-*H*) and δ 4.27 (C4-*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.82 (CH$_3$), 14.08 (CH$_3$), 36.26 (CH), 44.45 (CH), 46.40 (CH$_2$), 47.41 (CH), 48.30 (CH$_2$), 59.10 (C), 62.04 (CH$_2$), 62.50 (CH$_2$), 126.92 (CH), 127.44 (CH), 127.60 (CH), 127.92 (CH), 128.66 (CH), 128.84 (CH), 131.07 (CH), 131.17 (CH), 132.39 (C), 133.09 (C), 135.78 (C), 137.62 (C), 138.38 (C), 168.67 (C), 169.66 (C), 172.60 (C). Selected HMBC correlations are between δ 2.95 (C3-*H*H), 3.11 (C3-H*H*), 4.17 (C9a-*H*) and δ 36.26 (*C*3a), between δ 6.83 (C5-*H*) and δ 44.45 (*C*4), and between δ 4.17 (C9a-*H*), 8.09 (C8-*H*) and δ 59.10 (*C*9).; IR (KBr) 2978, 2935, 1731, 1685, 1492, 1450, 1292, 1231, 1094, 1036 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 45), 531 (M$^+$, 23), 430 (23), 149 (34), 91 (82), 57 (100%); HRMS (EI) *m/z* 531.1809 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813).

5j-*trans*: (0.43 mmol scale, DMF, r.t., 229 mg, 86%); R_f = 0.7 (hexane-AcOEt = 1 : 1); colorless crystals; mp 182.0-182.5 °C (hexane-AcOEt); 1H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 2.59 (dd, J = 9.7, 9.0 Hz, 1H), 2.92 (dddd, J = 13.5, 9.7, 7.8, 6.3 Hz, 1H), 3.24 (dd, J = 9.0, 7.8 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.77 (d, J = 15.0 Hz, 1H), 4.19 (dq, J = 10.7, 7.1 Hz, 1H), 4.29-4.50 (m, 4H), 4.90 (d, J = 15.0 Hz, 1H), 6.88-6.90 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 2.1 Hz, 1H), 7.21-7.32 (m, 8H), 7.51 (d, J = 2.1 Hz, 1H). Selected NOEs are between δ 2.92 (C3a-*H*) and δ 3.24 (C3-H*H*), between δ 3.44 (C9a-*H*) and δ 2.59 (C3-*H*H), 6.88-6.90 (*o*-H of C4-*Ar*), and between δ 2.59 (C3-*H*H) and δ 6.88-6.90 (*o*-H of

C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.96 (CH$_3$), 14.09 (CH$_3$), 36.35 (CH), 43.56 (CH), 46.14 (CH$_2$), 46.45 (CH), 47.18 (CH$_2$), 60.14 (C), 62.27 (CH$_2$), 62.80 (CH$_2$), 127.23 (CH), 127.44 (CH), 127.89 (CH), 128.63 (CH), 128.79 (CH), 130.14 (CH), 130.32 (CH), 132.61 (CH), 132.65 (C), 136.27 (C), 136.65 (C), 137.38 (C), 140.55 (C), 167.88 (C), 170.41 (C), 171.44 (C). Selected HMBC correlations are between δ 2.59 (C3-*H*H), 3.24 (C3-H*H*), 3.44 (C9a-*H*) and δ 36.35 (*C*3a), between δ 6.88-6.90 (*o*-H of C4-*Ar*) and δ 46.45 (*C*4), and between δ 3.44 (C9a-*H*), 7.51 (C8-*H*), 2.92 (C3a-*H*) and δ 60.14 (*C*9).; IR (KBr) 2979, 2902, 1741, 1699, 1596, 1492, 1434, 1362, 1250, 1199, 1115, 1026 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 19), 531 (M$^+$, 48), 428 (25), 191 (26), 91 (100%); HRMS (EI) *m/z* 531.1803, 533.1790 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813, 533.1783).

5j-*cis*: (1 mmol scale, toluene, 110 °C, 241 mg, 78% (**5j-*cis***:**5j-*trans*****=31:47), **5j-*cis*** was partially isolated by column chromatography. 84 mg, 16%); R$_f$ = 0.62 (benzene-ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 1.17 (t, *J* = 7.0 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 2.95 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.16 (dd, *J* = 9.8, 8.3 Hz, 1H), 3.31 (dddd, *J* = 9.8, 8.3, 7.0, 5.1 Hz, 1H), 4.09 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.17-4.29 (m, 5H), 4.35-4.49 (m, 2H), 6.80 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.91-6.93 (m, 2H), 7.03-7.06 (m, 2H), 7.00-7.02 (m, 4H), 7.13 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.16-7.23 (m, 3H), 7.25-7.34 (m, 3H), 8.26 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.80 (CH$_3$), 14.04 (CH$_3$), 35.88 (CH), 44.66 (CH), 46.36 (CH$_2$), 47.55 (CH), 48.29 (CH$_2$), 58.84 (C), 62.16 (CH$_2$), 62.66 (CH2), 127.41 (CH), 127.44 (CH), 127.51 (CH), 127.92 (CH), 128.63 (CH), 128.74 (CH), 128.80 (CH), 129.71 (CH), 130.76 (CH), 132.69 (C), 134.14 (C), 135.65 (C), 136.81 (C), 139.12 (C), 168.08 (C), 169.02 (C), 172.28 (C); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.779 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 2.69 (dd, *J* = 9.4, 8.2 Hz, 1H), 2.76 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.92 (dddd, *J* = 9.6, 8.2, 7.0, 4.7 Hz, 1H), 3.70 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.94 (d, *J* = 15.1 Hz, 1H), 3.99 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.07 (d, *J* = 15.1 Hz, 1H), 4.28 (d, *J* = 4.7 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.37-4.53 (m, 2H), 6.66 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.80-6.82 (m, 2H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.93 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.93-7.06 (m,

6H), 8.83 (d, J = 2.3 Hz, 1H). Selected NOEs are between δ 2.92 (C3a-H) and δ 4.39 (C9a-H), 4.28 (C4-H), and between δ 4.28 (C4-H) and δ 4.39 (C9a-H).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 13.57 (CH$_3$), 13.98 (CH$_3$), 36.20 (CH), 45.08 (CH), 46.36 (CH$_2$), 47.68 (CH), 48.07 (CH$_2$), 59.33 (C), 62.35 (CH$_2$), 62.46 (CH$_2$), 127.32 (CH), 127.51 (CH), 127.76 (CH), 128.06 (CH), 128.76 (CH), 128.83 (CH), 129.21 (CH), 129.91 (CH), 131.54 (CH), 132.97 (C), 135.12 (C), 136.49 (C), 137.56 (C), 139.73 (C) 168.26 (C), 169.43 (C), 171.79 (C). Selected HMBC correlations are between δ 2.69 (C3-HH), 2.76 (C3-HH), 4.39 (C9a-H), 4.28 (C4-H) and δ 36.20 (*C*3a), between δ 2.69 (C3-HH), 2.76 (C3-HH) and δ 45.08 (*C*4), and between δ 2.92 (C3a-H), 4.39 (C9a-H), 8.83 (C8-H) and δ 59.33 (*C*9).; IR (neat) 2982, 1731, 1693, 1596, 1495, 1475, 1445, 1365, 1240, 1173, 1101, 1038 cm^{-1}; MS (EI) *m/z* 533 (M$^+$, 30), 531 (M$^+$, 78), 310 (28), 91 (100%); HRMS (EI) *m/z* 531.1808, 533.1808 (calcd for C$_{31}$H$_{30}$ClNO$_5$ 531.1813, 533.1783).

5k-*trans*: (1 mmol scale, toluene, 110 °C, 292 mg, 55%); R$_f$ = 0.5 (hexane-AcOEt = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 2.53 (dd, J = 9.7, 9.2 Hz, 1H), 3.07 (dddd, J = 13.7, 9.7, 8.0, 6.4 Hz, 1H), 3.30 (dd, J = 9.2, 8.0 Hz, 1H), 3.34 (d, J = 13.7 Hz, 1H), 3.84 (d, J = 14.9 Hz, 1H), 4.16 (dq, J = 10.6, 7.1 Hz, 1H), 4.30-4.49 (m, 3H), 4.51 (d, J = 6.4 Hz, 1H), 4.87 (d, J = 14.9 Hz, 1H), 6.91 (dd, J = 7.7, 1.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 7.22-7.35 (m, 7H), 7.57 (dd, J = 8.0, 1.2 Hz, 1H), 8.14 (d, J = 8.7 Hz, 2H). Selected NOEs are between δ 3.07 (C3a-H) and δ 3.30 (C3-HH), 4.51 (C4-H) and between δ 2.53 (C3-HH) and δ 3.34 (C9a-H), 7.10 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.98 (CH$_3$), 14.15 (CH$_3$), 35.99 (CH), 43.87 (CH), 46.21 (CH$_2$), 46.74 (CH), 47.04 (CH$_2$), 60.09 (C), 62.19 (CH$_2$), 62.75 (CH$_2$), 123.73 (CH), 127.57 (CH), 127.72 (CH), 127.96 (CH), 128.69 (CH), 128.80 (CH), 130.94 (CH), 131.07 (CH), 131.17 (CH), 134.69 (C), 136.46 (C), 137.31 (C), 146.96 (C), 148.66 (C), 168.10 (C), 170.82 (C), 171.26 (C). Selected HMBC correlations are between δ 2.53 (C3-HH), 3.30 (C3-HH) and δ 35.99 (*C*3a), between δ 6.91 (C5-H), 7.10 (*o*-H of C4-*Ar*) and δ 46.74 (*C*4), and between δ 3.07 (C3a-H), 3.34 (C9a-H),

7.57 (C8-*H*) and δ 60.09 (*C*9).; IR (KBr) 2981, 1730, 1697, 1604, 1521, 1348, 1257, 1110, 1051, 1026 cm^{-1}; MS (FAB) *m/z* 565 ([M+Na]$^+$), 543 ([M+H]$^+$); HRMS (FAB) *m/z* 565.1956 (calcd for $C_{31}H_{30}N_2O_7Na$ [M+Na]$^+$ 565.1951), 543.2137 (calcd for $C_{31}H_{31}N_2O_7$ [M+H]$^+$ 543.2131).

Typical experimental procedure for 8 (Table 4-4, entry 2). To a solution of monomethyl fumarate (**6a**) (299 mg, 1 mmol) and N-benzyl 3,3-diphenyl-2-propen-1-amine (**4a**) (299 mg, 1 mmol) in toluene (1.6 mL) were added, Et$_3$N (0.14 mL, 101 mg, 1 mmol), HOBt (270 mg, 2 mmol), and EDCI (199 mg, 1 mmol) at 0 °C. The reaction mixture was stirred for 5 min. at 0 °C, and then heated at 110 °C and stirred for 20 h. The reaction mixture was diluted with CHCl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **8a** (194 mg, 47%).

8a: R$_f$ = 0.5 (hexane-ether = 1 : 4); colorless crystals; mp 164.5-165.5 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.60 (dddd, *J* = 13.7, 9.8, 6.8, 5.5 Hz, 1H), 2.74 (dd, *J* = 9.8, 8.7 Hz, 1H), 3.21 (dd, *J* = 8.7, 6.8 Hz, 1H), 3.25 (dd, *J* = 13.7, 11.5 Hz, 1H), 3.92 (d, *J* = 14.8 Hz, 1H), 3.93 (s, 3H), 4.02 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 5.5 Hz, 1H), 4.74 (d, *J* = 14.8 Hz, 1H), 6.97-6.99 (m, 2H), 7.02 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.15-7.31 (m, 10H), 7.41 (d, *J* = 7.8 Hz, 1H). Selected NOEs are between δ 2.60 (C3a-*H*) and δ 3.21 (C3-H*H*), 4.37 (C4-*H*), 4.02 (C9-*H*), and between δ 3.25 (C9a-*H*), 2.74 (C3-*H*H) and δ 6.97-6.99 (*o*-H of C4-*Ph*). Atom numbering is shown in Table 4-4.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 40.34 (CH), 40.41 (CH), 46.34 (CH$_2$), 46.69 (CH), 46.88 (CH), 47.69 (CH$_2$), 52.64 (CH$_3$), 126.97 (CH), 127.57 (CH), 127.63 (CH), 127.65 (CH), 127.79 (CH), 128.08 (CH), 128.47 (CH), 128.74 (CH), 130.36 (CH), 131.65 (CH), 133.92 (C), 136.53 (C), 138.45 (C), 140.84 (C), 173.40 (C), 173.90 (C). Selected HMBC correlations are between δ 4.02 (C9-*H*) and δ 40.34, 40.41 (*C*3a, *C*9a), between δ 2.74 (C3-*H*H), 3.21 (C3-H*H*), 2.60 (C3a-*H*), 4.02 (C9-*H*) and δ 46.69 (*C*4), and between δ 3.25 (C9a-*H*) and δ 46.88 (*C*9).; IR (KBr)

3024, 1735, 1685, 1494, 1430, 1309, 1205, 1161 cm^{-1}; MS (EI) m/z 411 (M$^+$, 47), 351 (23), 205 (22), 118 (24), 91 (100%); HRMS (EI) m/z 411.1845 (calcd for $C_{27}H_{25}NO_3$ 411.1834); Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 78.89; H, 6.22; N, 3.41.

7b: (1 mmol scale, THF, r.t., 188 mg, 89%); R_f = 0.6 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1.9:1) δ (ppm) 3.99 (d, J = 6.6 Hz, 2H×0.66, major rotamer), 4.18 (d, J = 7.0 Hz, 2H×0.34, minor rotamer), 4.47 (s, 2H×0.34), 4.66 (s, 2H×0.66), 5.90 (t, J = 6.6 Hz, 2H×0.66), 6.07 (t, J = 7.0 Hz, 2H×0.34), 6.73 (dq, J = 13.6, 1.7 Hz, 1H×0.66), 6.77-6.99 (m, 1H+1H×0.34), 7.06-7.41 (m, 15H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 45.32 (CH$_2$), 46.54 (CH$_2$), 49.76 (CH$_2$), 51.03 (CH$_2$), 122.59 (C, q, J_{FC} = 270 Hz), 122.61 (C, q, J_{FC} = 270 Hz), 122.86 (CH), 122.97 (CH), 126.67 (CH), 127.41 (CH), 127.55 (CH), 127.80 (CH), 128.02 (CH), 128.09 (CH), 128.12 (CH), 128.20 (CH), 128.22 (CH), 128.38 (CH), 128.43 (CH), 128.51 (CH), 128.67 (CH), 128.75 (CH), 129.00 (CH), 129.42-130.59 (m), 129.72 (CH), 129.76 (CH), 130.11 (CH), 135.95 (C), 136.65 (C), 138.19 (C), 138.75 (C), 140.98 (C), 141.39 (C), 145.68 (C), 163.55 (C), 163.66 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -64.72 (d, J_{FH} = 5.7 Hz, 3F×0.66), -65.01 (d, J_{FH} = 5.7 Hz, 3F×0.34); IR (neat) 3060, 1681, 1633, 1495, 1445, 1303, 1266, 1132 cm^{-1}; MS (EI) m/z 421 (M$^+$, 18), 330 (29), 191 (100%); HRMS (EI) m/z 421.1656 (calcd for $C_{26}H_{22}F_3NO$ 421.1653).

8c: (1 mmol scale, toluene, 110 °C, 237 mg, 48%); R_f = 0.5 (hexane-ether = 1 : 4); pale yellow crystals; mp 84-85 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.68-2.72 (m, 1H), 3.13-3.26 (m, 3H), 3.81 (d, J = 14.8 Hz, 1H), 4.41 (d, J = 4.1 Hz, 1H), 4.92 (d, J = 14.8 Hz, 1H), 6.83-6.85 (m, 2H), 7.10 (dd, J = 7.5, 1.9 Hz, 1H), 7.15-7.17 (m, 2H), 7.22-7.39 (m, 7H), 7.91 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 36.74 (CH, q, J_{FC} = 1.5 Hz), 40.39 (CH), 45.95 (CH$_2$), 46.45 (CH), 46.80 (CH$_2$), 56.47 (C, septet, J_{FC} = 26 Hz), 123.59 (C, q, J_{FC} = 288 Hz), 125.01 (C, q, J_{FC} = 287 Hz), 127.41 (CH), 127.51 (CH), 127.66 (CH), 127.89 (CH), 128.73 (CH), 128.77 (CH), 129.90 (CH), 130.05 (CH), 130.97 (CH, septet, J_{FC} = 3.8 Hz), 132.12 (CH), 136.34 (C), 139.51 (C), 140.85 (C), 167.96 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -61.15 (q, J_{FH} = 6.9 Hz, 3F), -64.20 (q, J_{FH} =

6.9 Hz, 3F); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 2.31 (dd, J = 9.5, 8.6 Hz, 1H), 2.65 (dd, J = 8.6, 7.4 Hz, 1H), 2.75 (dddd, J = 13.9, 9.5, 7.4, 5.7 Hz, 1H), 3.12 (d, J = 13.9 Hz, 1H), 3.14 (d, J = 15.0 Hz, 1H), 3.73 (d, J = 5.7 Hz, 1H), 4.82 (d, J = 15.0 Hz, 1H), 6.64-6.66 (m, 2H), 6.72 (dd, J = 7.4, 2.0 Hz, 1H). 6.91-7.10 (m, 9H), 7.98 (d, J = 7.2 Hz, 1H). Selected NOEs are between δ 2.75 (C3a-*H*), 2.65 (C3-H*H*) and δ 3.73 (C4-*H*), between δ 2.31 (C3-*H*H) and δ 3.12 (C9a-*H*) and between δ 2.31 (C3-*H*H), 3.12 (C9a-*H*) and δ 6.64-6.66 (*o*-H of C4-*Ph*).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 36.90 (CH, q, J_{FC} = 2.3 Hz), 40.66 (CH), 45.47 (CH2), 46.28 (CH), 46.47 (CH$_2$), 56.93 (C, septet, J_{FC} = 26 Hz), 124.88 (C, q, J_{FC} = 289 Hz), 125.85 (C, q, J_{FC} = 289 Hz), 127.33 (CH), 127.62 (CH), 127.64 (CH), 128.00 (CH), 128.76 (CH), 128.81 (CH), 129.82 (CH), 130.23 (CH), 131.27 (CH, septet, J_{FC} = 3.8 Hz), 132.29 (CH), 137.36 (C), 140.15 (C), 141.32 (C), 166.98 (C). Selected HMBC correlations are between δ 2.65 (C3-H*H*), 3.73 (C4-*H*) and δ 36.90 (*C*3a), between δ 2.65 (C3-H*H*), 3.73 (C4-*H*) and δ 40.66 (*C*9a), and between δ 3.12 (C9a-*H*) and δ 56.93 (*C*9).; IR (KBr) 3030, 2888, 1711, 1496, 1258, 1200, 1161 cm^{-1}; MS (EI) *m/z* 489 (M$^+$, 61), 91 (100%); HRMS (EI) *m/z* 489.1527 (calcd for C$_{27}$H$_{21}$F$_6$NO 489.1527).

8d: (1 mmol scale, THF, 60 °C, 388 mg, 80%); R$_f$ = 0.6 (hexane-ether = 1 : 4); colorless crystals; mp 202-203 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.56 (dddd, J = 13.8, 9.9, 7.0, 5.5 Hz, 1H), 2.72 (dd, J = 9.9, 9.2 Hz, 1H), 3.15 (dd, J = 13.8, 11.6 Hz, 1H), 3.21 (dd, J = 9.2, 7.0 Hz, 1H), 3.94 (s, 3H), 3.95 (d, J = 14.8 Hz, 1H), 3.96 (d, J = 11.6 Hz, 1H), 4.31 (d, J = 5.5 Hz, 1H), 4.71 (d, J = 14.8 Hz, 1H), 6.90 (d-like, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.14-7.17 (m, 3H), 7.24-7.32 (m, 5H), 7.39-7.40 (m, 1H). Selected NOEs are between δ 2.56 (C3a-*H*) and δ 3.21 (C3-H*H*), 4.31 (C4-*H*), 3.96 (C9-*H*), between δ 3.15 (C9a-*H*) and δ 2.72 (C3-*H*H), and between δ 3.15 (C9a-*H*), 2.72 (C3-*H*H) and δ 6.90 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 39.99 (CH), 40.16 (CH), 45.63 (CH), 46.40 (CH2), 46.54 (CH), 47.43 (CH2), 52.89 (CH$_3$), 127.70 (CH), 127.73 (CH), 128.08 (CH), 128.27 (CH), 128.79 (CH), 131.49 (CH), 132.69 (CH), 133.22 (C), 133.51 (C), 135.63 (C), 136.30 (C), 136.56 (C), 138.70 (C), 172.76 (C), 173.17 (C).

Selected HMBC correlations are between δ 2.72 (C3-*H*H), 3.21 (C3-H*H*), 3.15 (C9a-*H*), 3.96 (C9-*H*) and δ 40.16 (*C*3a), between δ 3.21 (C3-H*H*), 3.15 (C9a-*H*) and δ 45.63 (*C*4), and between δ 3.15 (C9a-*H*) and δ 46.54 (*C*9).; IR (KBr) 2946, 2912, 1740, 1698, 1560, 1485, 1436, 1273, 1118, 1014 cm^{-1}; MS (EI) *m/z* 481 (M$^+$, 69), 479 (M$^+$, 100), 419 (27), 118 (34%); HRMS (EI) *m/z* 479.1049, 481.1028 (calcd for $C_{27}H_{23}Cl_2NO_3$ 479.1055, 481.1025); Anal. Calcd for $C_{27}H_{23}Cl_2NO_3$: C, 67.51; H, 4.83; N, 2.92. Found: C, 67.51; H, 4.84; N, 2.95.

7e: (1 mmol scale, THF, r.t., 376 mg, 77%); R_f = 0.8 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1.3:1) δ (ppm) 4.00 (d, *J* = 6.4 Hz, 2H×0.57, major rotamer), 4.16 (d, *J* = 6.8 Hz, 2H×0.43, minor rotamer), 4.49 (s, 2H×0.43), 4.66 (s, 2H×0.57), 5.87 (t, *J* = 6.4 Hz, 1H×0.57), 6.04 (t, *J* = 6.8 Hz, 1H×0.43), 6.72 (dq, J_{HH} = 15.2, J_{FH} = 1.8 Hz, 1H×0.57), 6.79-6.90 (m, 1H), 6.96-7.36 (m, 13H+1H×0.43); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 45.31 (CH$_2$), 46.42 (CH$_2$), 49.78 (CH$_2$), 51.28 (CH$_2$), 122.46 (C, q, J_{FC} = 270 Hz), 122.49 (C, q, J_{FC} = 270 Hz), 124.07 (CH), 124.17 (CH), 126.57 (CH), 127.78 (CH), 127.96 (CH, q, J_{FC} = 6.1 Hz), 128.05 (CH), 128.30 (CH), 128.34 (CH), 128.51 (CH), 128.55 (CH), 128.67 (CH), 128.69 (CH), 128.92 (CH), 128.96 (CH), 129.91 (CH, q, J_{FC} = 35 Hz), 130.10 (CH, q, J_{FC} = 35 Hz), 130.93 (CH), 133.66 (C), 133.76 (C), 134.11 (C), 134.41 (C), 135.67 (C), 135.99 (C), 136.46 (C), 136.59 (C), 138.96 (C), 139.42 (C), 142.98 (C), 143.14 (C), 163.36 (C), 163.57 (C); 19F NMR (376 MHz, CDCl3) δ (ppm) -64.67 (d, J_{FH} = 5.7 Hz, 3F×0.57), -64.90 (d, J_{FH} = 4.6 Hz, 3F×0.43); IR (neat) 3064, 1681, 1638, 1493, 1303, 1134, 1091, 1014 cm^{-1}; MS (EI) *m/z* 491 (M$^+$, 13), 489 (M$^+$, 20), 400 (29), 398 (41), 261 (70), 259 (100%); HRMS (EI) *m/z* 489.0880, 491.0849 (calcd for $C_{26}H_{20}Cl_2F_3NO$ 489.0874, 491.0845).

8e: (0.5 mmol scale, toluene in a closed vessel, 160 °C, 94 mg, 38%); R_f = 0.7 (hexane-AcOEt = 1 : 1); colorless crystals; mp 198.5-199.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.56 (dddd, *J* = 14.2, 9.7, 6.3, 4.5 Hz, 1H), 2.62 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.93 (dd, *J* = 9.7, 9.2 Hz, 1H), 3.22 (dd, *J* = 9.2, 6.3 Hz, 1H), 4.05 (dq, *J* = 9.7, JFC = 9.2 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 4.27 (d,

J = 4.5 Hz, 1H), 4.73 (d, J = 14.8 Hz, 1H), 6.88 (d-like, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 7.18-7.20 (m, 2H), 7.25-7.33 (m, 6H), 7.63 (bs, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 37.47 (CH), 42.04 (CH), 43.30 (CH, q, J_{FC} = 27 Hz), 45.49 (CH), 46.63 (CH$_2$), 46.78 (CH$_2$), 126.59 (C, q, J_{FC} = 282 Hz), 128.12 (CH), 128.76 (CH), 128.81 (CH), 128.85 (CH), 130.02 (CH, q, J_{FC} = 3.1 Hz), 131.22 (CH), 132.09 (C, q, J¬FC = 1.6 Hz), 132.42 (CH), 133.41 (C), 133.56 (C), 136.30 (C), 136.98 (C), 138.00 (C), 171.85 (C); ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -65.57 (d, J_{FH} = 9.2 Hz); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 1.57 (dddd, J = 14.5, 10.5, 6.4, 4.9 Hz, 1H), 2.23 (dd, J = 10.5, 9.0 Hz, 1H), 2.30 (dd, J = 14.5, 10.0 Hz, 1H), 2.49 (dd, J = 9.0, 6.4 Hz, 1H), 3.30 (d, J = 4.9 Hz, 1H), 3.38 (d, J = 14.9 Hz, 1H), 3.74 (dq, J = 10.0, JFH = 8.9 Hz, 1H), 4.81 (d, J = 14.9 Hz, 1H), 6.34 (d, J = 8.3 Hz, 1H), 6.43 (d, J = 8.5 Hz, 2H), 6.94 (dd, J = 8.3, 2.1 Hz, 1H), 6.98 (d-like, J = 8.5 Hz, 2H), 7.05-7.16 (m, 5H), 7.58 (s, 1H). Selected NOEs are between δ 1.57 (C3a-*H*) and δ 2.49 (C3-H*H*), 3.30 (C4-*H*), 3.74 (C9-*H*), between δ 2.49 (C3-H*H*) and δ 3.30 (C4-*H*), and between δ 2.30 (C9a-*H*) and δ 6.43 (*o*-H of C4-*Ar*).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 37.26 (CH), 41.52 (CH), 43.38 (CH, q, J_{FC} = 27 Hz), 45.23 (CH), 45.82 (CH$_2$), 46.50 (CH$_2$), 127.25 (C, q, J_{FC} = 282 Hz), 127.89 (CH), 128.33 (CH). 128.49 (CH), 128.74 (CH), 128.91 (CH), 130.49 (CH, q, J_{FC} = 3.1 Hz), 131.31 (CH). 132.38 (CH), 132.68 (C, q, J_{FC} = 1.6 Hz), 133.37 (C), 133.49 (C), 137.30 (C), 137.49 (C), 138.27 (C), 170.91 (C). Selected HMBC correlations are between δ 2.23 (C3-*H*H), 2.49 (C3-H*H*), 2.30 (C9a-*H*), 3.30 (C4-*H*) and δ 41.52 (*C*3a), between δ 2.23 (C3-*H*H), 2.30 (C9a-*H*), 1.57 (C3a-*H*) and δ 45.23 (*C*4), and between C 2.30 (C9a-*H*) and C 43.38 (*C*9).; IR (KBr) 2912, 1696, 1491, 1243, 1165, 1097 cm^{-1}; MS (EI) *m/z* 491 (M[+], 59), 489 (M[+], 88), 91 (100%); HRMS (EI) *m/z* 489.0880, 491.0862 (calcd for C$_{26}$H$_{20}$Cl$_2$F$_3$NO 489.0874, 491.0845).

8f: (1 mmol scale, benzene, 80 °C, 298 mg, 53%); R$_f$ = 0.3 (hexane-ether = 1 : 4); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.68 (dd, J = 9.4, 9.1 Hz, 1H), 3.04 (d, J = 13.9 Hz, 1H), 3.15 (dddd, J = 13.9, 9.4, 7.2, 5.3 Hz, 1H), 3.25 (dd, J = 9.1, 7.2, 1H), 3.84 (d, J = 14.8 Hz,

1H), 4.36 (d, J = 5.3 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 6.76 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 1H), 7.14-7.16 (m, 2H), 7.24-7.34 (m, 6H), 7.89 (s, 1H). Selected NOEs are between δ 3.15 (C3a-H) and δ 3.25 (C3-HH), and between δ 3.15 (C3a-H) and δ 4.36 (C4-H), between δ 2.68 (C3-HH) and δ 3.04 (C9a-H), and between δ 2.68 (C3-HH), 3.04 (C9a-H) and δ 6.76 (o-H of C4-Ar).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 36.56 (CH, q, J_{FC} = 2.3 Hz), 40.08 (CH), 45.38 (CH), 45.72 (CH), 46.85 (CH$_2$), 56.37 (C, septet, J_{FC} = 26 Hz), 123.75 (C, q, J_{FC} = 288 Hz), 124.70 (C, q, J_{FC} = 288 Hz), 127.76 (CH), 127.88 (CH), 128.81 (CH), 128.99 (C), 129.05 (CH), 130.50 (CH), 130.95 (CH, septet, J_{FC} = 3.7 Hz), 131.17 (CH), 133.09 (CH), 133.67 (C), 133.74 (C), 136.08 (C), 137.39 (C), 138.94 (C), 167.24 (C). Selected HMBC correlations are between δ 2.68 (C3-HH), 3.25 (C3-HH), 3.04 (C9a-H), 4.36 (C4-H) and δ 36.56 (C3a), between δ 3.25 (C3-HH), 4.36 (C4-H), 3.15 (C3a-H) and δ 40.08 (C9a), and between δ 3.04 (C9a-H) and δ 56.37 (C9).; ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) -61.06 (q, J_{FF} = 6.9 Hz), -64.31 (q, J_{FF} = 6.9 Hz); IR (KBr) 3031, 2888, 1711, 1596, 1491, 1259, 1203, 1163, 1015 cm^{-1}; MS (EI) m/z 559 (M$^+$, 43), 557 (M$^+$, 63), 91 (100%); HRMS (EI) m/z 557.0755, 559.0730 (calcd for C$_{27}$H$_{19}$Cl$_2$F$_6$NO 557.0748, 559.0718).

7a,c,d,f are unstable and decompose to give complex mixtures gradually. They are freshly prepared and used immediately in Table 4-5. For **7a**, 1H and ^{13}C NMR and mass spectra and for **7d**, ^{1}H and ^{13}C NMR spectra were measured. For **7c** and **7f**, copy of ^{1}H NMR are shown in Figure 4-1, 4-2.

7a: (1 mmol scale, THF, r.t., 318 mg, 77%); R$_f$ = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1.5:1) δ (ppm) 3.72 (s, 3H×0.4, minor rotamer), 3.74 (s, 3H×0.6, major rotamer), 4.01 (d, J = 6.4 Hz, 2H×0.6), 4.17 (d, J = 7.0 Hz, 2H×0.4), 4.48 (s, 2H×0.4), 4.62 (s, 2H×0.6), 5.91 (t, J = 6.4 Hz, 1H×0.6), 6.08 (t, J = 7.0 Hz, 1H×0.4), 6.89 (d, J = 15.2 Hz, 1H×0.6), 6.94 (d, J = 15.2 Hz, 1H×0.4), 6.97 (dd, J =7.5, 1.9 Hz, 2H×0.4), 7.05-7.13 (m, 4H+2H×0.6), 7.20-7.40 (m, 9H), 7.30 (d, J = 15.2 Hz, 1H×0.6), 7.44 (d, J = 15.2 Hz, 1H×0.4); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 44.83 (CH$_2$), 46.37 (CH$_2$), 49.19 (CH$_2$), 50.83 (CH$_2$), 51.96 (CH$_3$), 52.02 (CH$_3$), 123.11 (CH), 123.16 (CH), 126.67 (CH), 127.23 (CH), 127.34 (CH), 127.39 (CH), 127.46

(CH), 127.69 (CH), 127.80 (CH), 127.83 (CH), 128.02 (CH), 128.15 (CH), 128.22 (CH), 128.34 (CH), 128.41 (CH), 128.47 (CH), 128.70 (CH), 129.56 (CH), 129.61 (CH), 131.29 (CH), 131.54 (CH), 133.86 (CH), 133.89 (CH), 135.99 (C), 136.69 (C), 138.20 (C), 138.61 (C), 140.89 (C), 141.28 (C), 145.21 (C), 145.38 (C), 164.49 (C), 164.57 (C), 165.80 (C), 165.89 (C); MS (EI) m/z 411 (M$^+$, 28), 298 (18), 191 (100%); HRMS (EI) *m/z* 411.1845 (calcd for C$_{27}$H$_{25}$NO$_3$ 411.1834).

7c: (1 mmol scale, THF, r.t., 149 mg, 39%); R$_f$ = 0.6 (hexane-ether = 1 : 1); pale yellow oil.
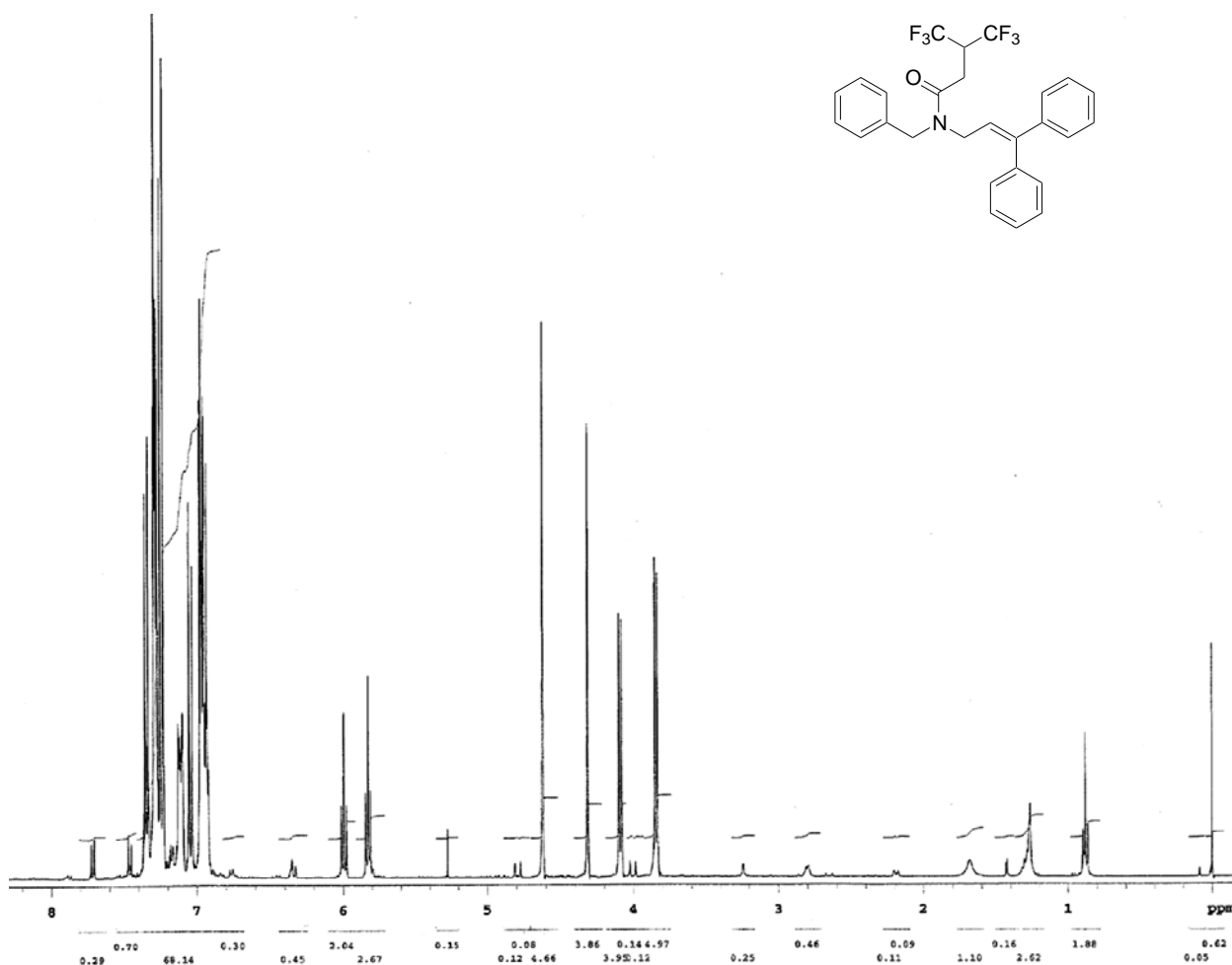
Figure 4-1. ^{1}H NMR of **7c**.

7d: (1 mmol scale, THF, r.t., 415 mg, 86%); R$_f$ = 0.7 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1:1) δ (ppm) 3.76 (s, 3H×0.5), 3.77 (s, 3H×0.5), 4.00 (d, *J* = 6.4 Hz, 2H×0.5), 4.13 (d, *J* = 6.8 Hz, 2H×0.5), 4.51 (s, 2H×0.5), 4.63 (s, 2H×0.5), 5.87 (t, *J* = 6.4 Hz, 1H×0.5), 6.03 (t, *J* = 6.8 Hz, 1H×0.5), 6.87 (d, *J* = 15.2 Hz, 1H), 6.92 (d, *J* = 15.2 Hz,

1H), 6.95-7.05 (m, 4H+2H×0.5), 7.09-7.12 (m, 2H×0.5), 7.18-7.35 (m, 5H+2H×0.5+1H×0.5), 7.37 (d-like, J = 8.4 Hz, 2H×0.5), 7.42 (d, J = 15.2 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 45.11 (CH$_2$), 46.52 (CH$_2$), 49.54 (CH$_2$), 51.36 (CH$_2$), 52.15 (CH$_3$), 124.45 (CH), 126.74 (CH), 127.72 (CH), 128.00 (CH), 128.34 (CH), 128.37 (CH), 128.53 (CH), 128.58 (CH), 128.68 (CH), 128.93 (CH), 130.99 (CH), 131.03 (CH), 131.61 (CH), 131.88 (CH), 133.68 (C), 133.73 (C), 133.76 (CH), 134.09 (C), 134.27 (C), 135.90 (C), 136.22 (C), 136.65 (C), 136.69 (C), 139.05 (C), 139.51 (C), 142.85 (C), 143.14 (C), 164.64 (C), 164.82 (C), 165.89 (C), 165.96 (C).

7f: (1 mmol scale, THF, r.t., 320 mg, 57%); Rf = 0.7 (hexane-ether = 1 : 4); pale yellow oil.
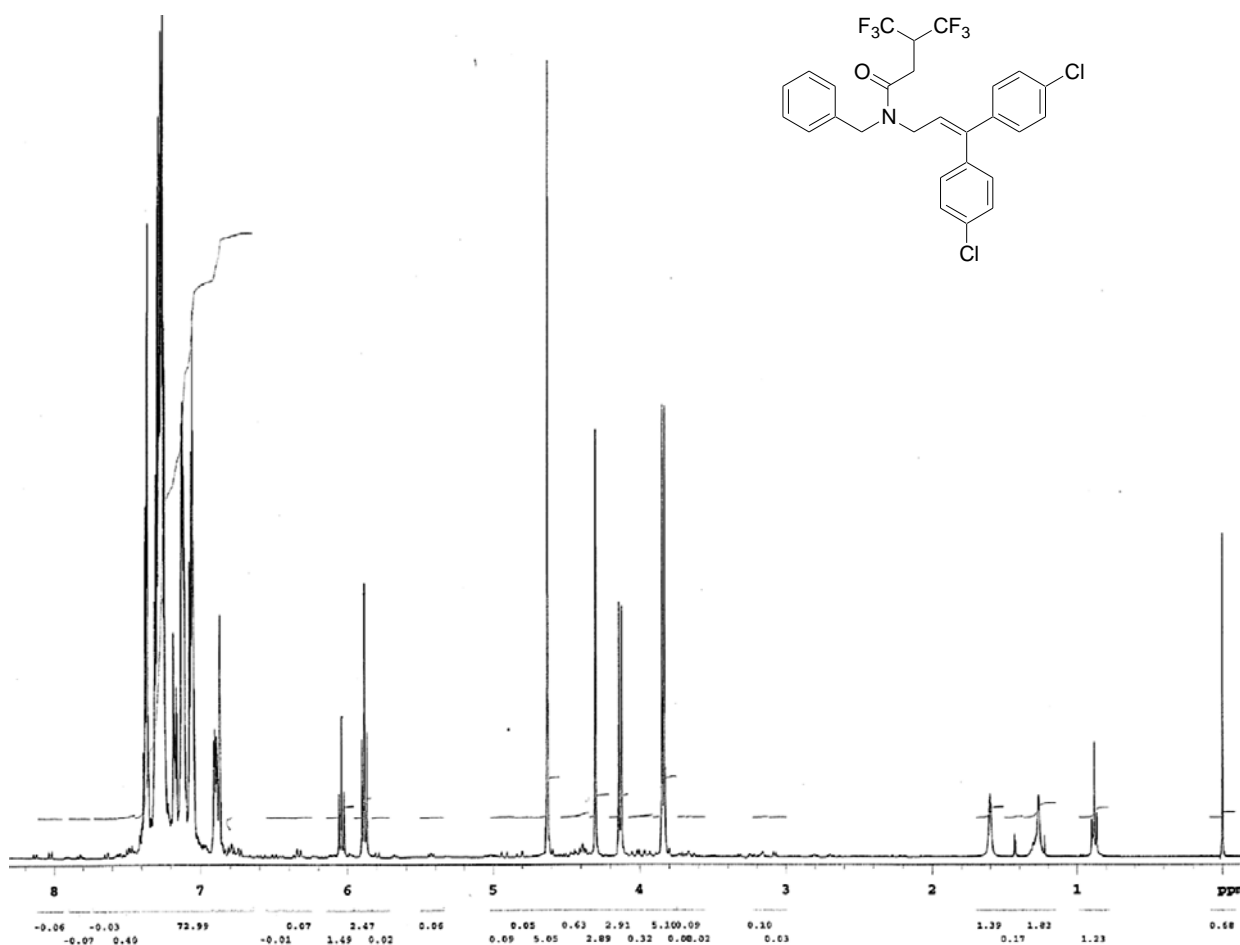
Figure 4-2. ^{1}H NMR of **7f**.

Transformation of 7 to 8 (Table 4-5, entry 8): To a solution of **7d** (415 mg, 0.86 mmol, freshly prepared under the conditions of Table 4-4, entry 9) in THF (2 mL) was added Et$_3$N (0.12 mL, 87 mg, 0.86 mmol). The mixture was stirred at 60 °C for 20 h. The reaction mixture was

concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **8d** (365 mg, 88%).

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Chapter 5

Sequential Intramolecular Diels-Alder Reaction of 3-Heteroaryl-2-propenylamides of Ethenetricarboxylate

5-1 Introduction

 The development of the synthetic strategies of linearly fused heterocyclic ring systems has attracted significant attention because of their widespread occurrence in biologically active compounds. [1] The intramolecular Diels-Alder (IMDA) reaction of vinylfurans and the heteroaromatic analogues such as vinyl pyrroles, thiophenes,[2,3] and imidazoles,[4] has been used to construct the linearly fused tricyclic heterocycles.[5]

 In chapters 3 and 4, reactions of highly electron-deficient alkenic carboxylic acid, 1,1-diethyl 2-hydrogen ethenetricarboxylate **1**, with *E*- or *Z*-cinnamylamines and 3,3-diary-2-propenylamines under the amide formation conditions gave tricyclic compounds in sequential amide formation/IMDA reaction/rearomatization process (Scheme 5-1). Reaction of **1** with *E*-cinnamylamines bearing electron-withdrawing groups under the amide formation conditions gave *trans*-fused tetrahydrobenz[*f*]isoindolines. The reaction of **1** with *Z*-cinnamylamines on heating at 80-110 °C gave [4 + 2] cycloadducts, *cis*-fused tricyclic compounds as the major products. Reaction of **1** with 3,3-diaryl-2-propen-1-amines gave *cis*- and *trans*-fused tricyclic compounds selectively, depending on the substituents on the benzene ring, reaction temperature, and solvent. The reaction mechanism of the formation of *cis*- and *trans*-fused rings was discussed.

 In order to extend the stereoselective construction of *cis*- and *trans*-fused linearly fused tricyclic compounds by IMDA reaction of styrenes (vinyl benzene) to the reaction of vinyl heteroarenes, the reaction of **1** with 3-heteroaryl-2-propenylamines has been studied in this work. Substituted regioisomers of furan and thiophene as examples of five-membered and electron-rich

heteroarenes and pyridine as an example of six-membered and electron-poor heteroarenes have been examined.[6] Lower aromaticity of the heterocycles than benzene may effect the reaction.[7] It is also desirable to develop new efficient reactions using furans as renewable resources.[8] The origin of stereoselectivity of the fused rings has been examined by the DFT calculations.
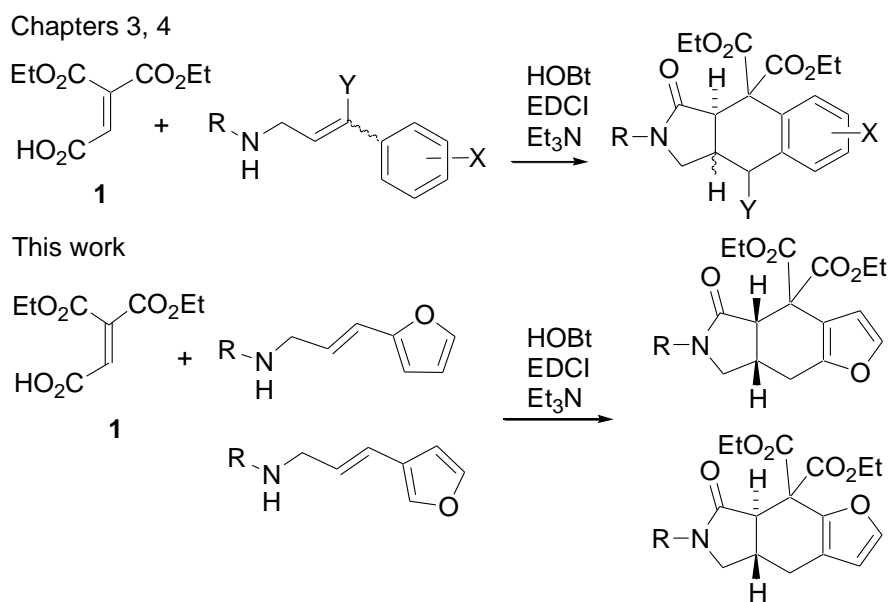

Scheme 5-1. The reaction of 3-aryl-2-propenylamines and ethenetricarboxylate.

5-2 Results and Discussion

Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and furan substrates in the presence of EDCI/HOBt/Et$_3$N were examined. Reaction of **1** and E-3-(2-furyl)-2-propenylamines **2a-b** in the presence of EDCI/HOBt/Et$_3$N in THF at room temperature gave a complex mixture and the possible [2 + 2] cycloadducts were not detected. The reaction of **1** and **2a-b** in benzene, DME, DMF and toluene at 80-110 °C gave [4 + 2] cycloadducts, furo[$2,3$-f]isoindoles **3a-b** as the major products (Table 5-1). The products **3a-b** are unstable and decomposed gradually at room temperature. Treatment of crude **3a-b** with 1 M HCl in ether gave the furan-reproduced products **4a-b** (Table 5-2). The cis-fused stereochemistry of **4a-b** was determined by observed NOEs between C7a-H and C4a-H. The reaction of **2a** in ClCH$_2$CH$_2$Cl at 80-110 °C gave **4a** directly,

probably because of generation of HCl *in situ* under the reaction conditions. [9] The stereochemistry of unstable **3a-b** was deduced from their crude NMR and the proposed mechanism shown below.

Table 5-1. Reactions of 1,1-diethyl ethenetricarboxylate **1** and (*E*)-3-(2-furyl)-2-propenylamines **2**.

3a-b

4a-b
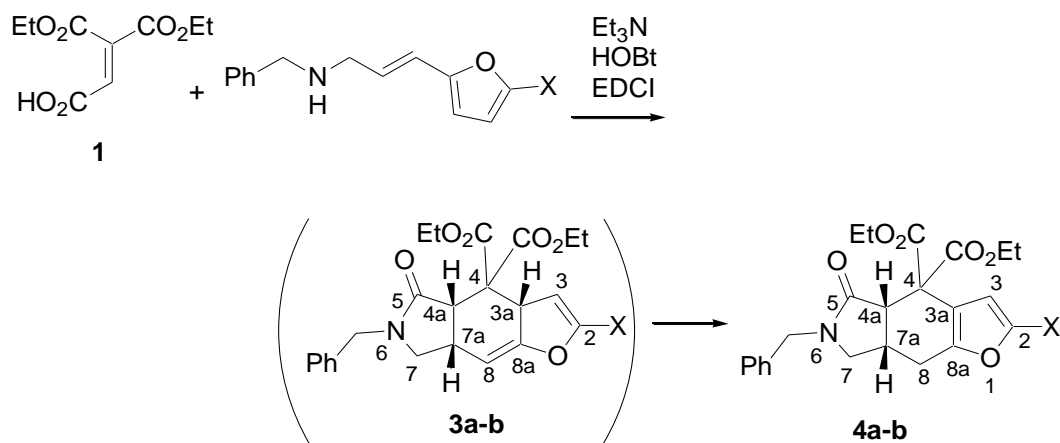
Entry	2	X	Solvent	Temp.	Product	Yield (%)
1	**2a**	H	THF	r.t.	[a]	-
2	**2a**	H	ClCH₂CH₂Cl	80 °C	**4a**	69
3	**2a**	H	Benzene	80 °C	**3a**	ca. 61
4	**2a**	H	DME	80 °C	**3a**	ca. 71
5	**2a**	H	DMF[b]	80 °C	**3a**	ca. 71
6	**2b**	Br	THF	r.t.	[a]	-
7	**2b**	Br	ClCH₂CH₂Cl	80 °C	**3b**	ca. 65
8	**2b**	Br	Benzene	80 °C	**3b**	ca. 65
9	**2b**	Br	Toluene	110 °C	**3b**	ca. 73

[a] A complex mixture. [b] The reaction in DMF at room temperature gave a complex mixture.

Table 5-2. Transformation of **3** to **4**.

Entry	3	X	HCl	Solvent	Temp.	Product	Yield (%)
1	**3a**	H	1 eq	ClCH₂CH₂Cl	80 °C	**4a**	78
2	**3b**	Br	0.1 eq	ClCH₂CH₂Cl	80 °C	**4b**	74
3	**3b**	Br	0.1 eq	Benzene	80 °C	**4b**	65

The reaction of **1** and *E*-3-(2-furyl)-2-propenylamine **5a** in THF at room temperature gave [4 + 2] cycloadduct, furo[*2,3-f*]isoindole **6a** as the major products (Table 5-3). The product **6a** is unstable and decomposed gradually at room temperature. The reaction of **1** and *E*-3-(2-furyl)-2-propenylamines **5a-b** in ClCH₂CH₂Cl, DME, PhCF₃, benzene, and toluene at 80-110 °C gave *trans*-fused furan-reproduced products **7a-b** directly as the major products. The *trans*-fused stereochemistry of **7a-b** was determined by observed NOEs between C4a-*H* and C5-H$^\alpha$*H*$^\beta$, between C5-*H*$^\alpha$H$^\beta$ and C4-*H*$^\alpha$H$^\beta$, and between C4-*H*$^\alpha$H$^\beta$ and C7a-*H*. The stereochemistry of unstable **6a** was deduced from the crude NMR and the proposed mechanism shown below.

Although the initial cycloadducts **3** and **6** are unstable, they were isolated as crude forms. On the other hand, the corresponding initial cycloadducts for styrenes were not detected under the reaction conditions.[10] This is probably because the aromaticity strength of heteroarenes is comparatively lower than that of benzene. A few initial adducts of IMDA reactions of vinyl heteroarenes were isolated and characterized.[3, 4]

Table 5-3. Reactions of 1,1-diethyl ethenetricarboxylate **1** and (*E*)-3-(3-furyl)-2-propenylamines **5**.
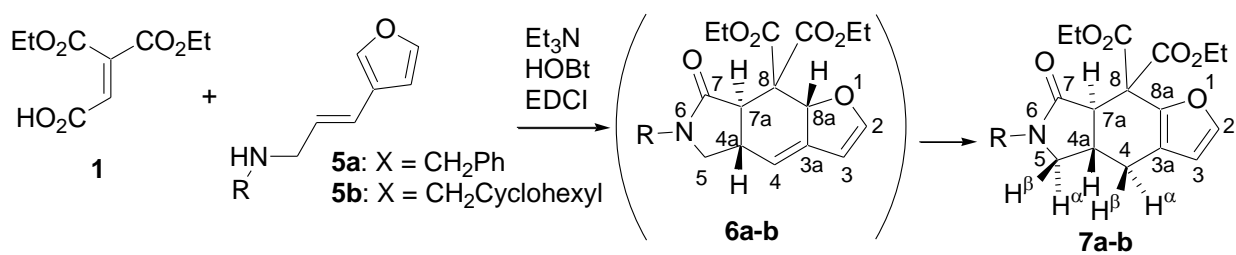
Entry	5	R	Solvent	Temp.	product	Yield (%)
1	**5a**	CH$_2$Ph	THF	r.t.	**6a**	ca. 59[a]
2	**5a**	CH$_2$Ph	CH$_2$ClCH$_2$Cl	80 °C	**7a**	78
3	**5a**	CH$_2$Ph	DME	80 °C	**7a**	52
4	**5a**	CH$_2$Ph	PhCF$_3$	80 °C	**7a**	65
5	**5a**	CH$_2$Ph	Benzene	80 °C	**7a**	70
6	**5a**	CH$_2$Ph	Toluene	110 °C	**7a**	72
7	**5b**	CH$_2$Cyclohexyl	Benzene	80 °C	**7b**	48
8	**5b**	CH$_2$Cyclohexyl	Toluene	110 °C	**7b**	39

[a] Product **6a** is unstable and decomposes to give complex mixtures gradually.

Next, the reaction of **1** and other 3-heteroaryl-2-propenylamines **8**, **9**, and **10** in the presence of the amide condensation reagents was examined (Scheme 5-2).
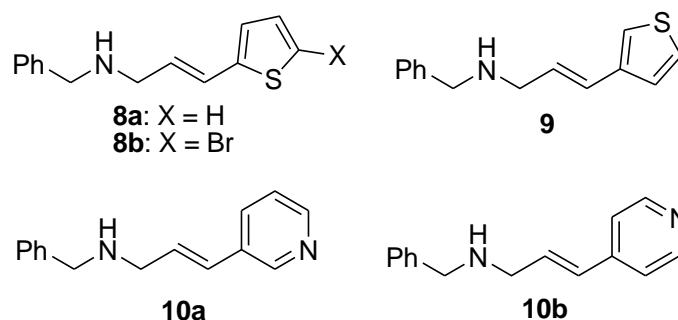
Scheme 5-2 3-Heteroaryl-2-propenylamines **8**, **9**, and **10**.

The reactions of 3-(2-thiophenyl)-2-propen-1-amines **8a,b** and 3-(-3-thiophenyl) -2-propen-1-amine **9** only gave complex mixtures under the various reaction conditions, probably

because the initial [4 + 2] cycloadducts, further intermediates or thiophene reproduced products for thiophene derivatives are unstable under the reaction conditions.

Among them, the reaction of **1** and **8b** at room temperature gave ketone derivative **11** as an isolable product in 45% yield (Scheme 5-3). The similar C8-oxidized products may be formed for other substrates such as **2**, **5**, and **8a**, probably by oxidation with adventitious oxygen in situ. Addition of a radical scavenger such as TEMPO or the reaction under air was also attempted. However, the reproduced results and isolation of the oxidized products for the other substrates could not be achieved. The stereochemistry of **11** was determined as *cis*-fused by observed NOEs (in C_6D_6) between C7a-*H* and C4a-*H*, similar to products **4a-b** from 3-(2-furyl)-2-propen-1-amines **2a-b**.
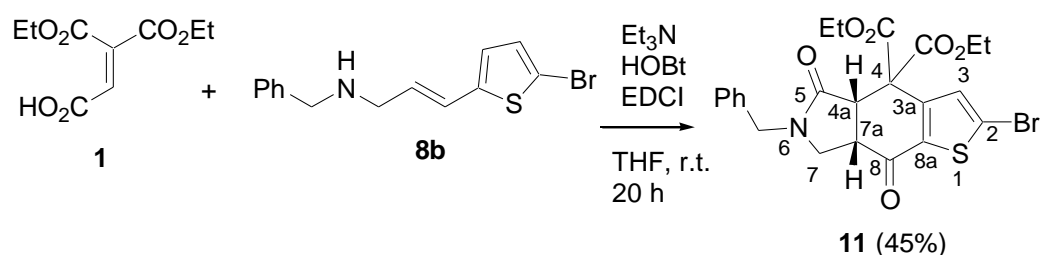
Scheme 5-3. The reaction of **1** and **8b**.

Reaction of **1** and 3-(3-pyridinyl)-2-propen-1-amine **10a** with EDCI/HOBt/Et₃N at room temperature, 60 °C and 80 °C gave HOBt-incorporated 3,4-*trans*-pyrrolidine **12** as a single diastereomer in 61% yield selectively (Scheme 5-4). On the other hand, the reaction of 3-(4-pyridinyl)-2-propen-1-amine **10b** only gave complex mixtures

Since the nitrogen is more electronegative than carbon, the pyridine ring is electron-deficient.[11] The reaction of **10a** proceeded similarly to the styrene derivative with electron-withdrawing *m*-nitro group. The stereochemistry of **12** was deduced as shown in Scheme 5-4, similarly to the proposed mechanism for formation of HOBt adduct from *m*-nitrocinnamylamide.[10a] The O-C bond formation and C-C bond formation from the

intermediate amide occurred concertedly to lead to a cyclized product **12**. Intermolecular HOBt

nucleophilic attack from outside may lead to 3,4-*trans* cyclized product **12** by steric reason.
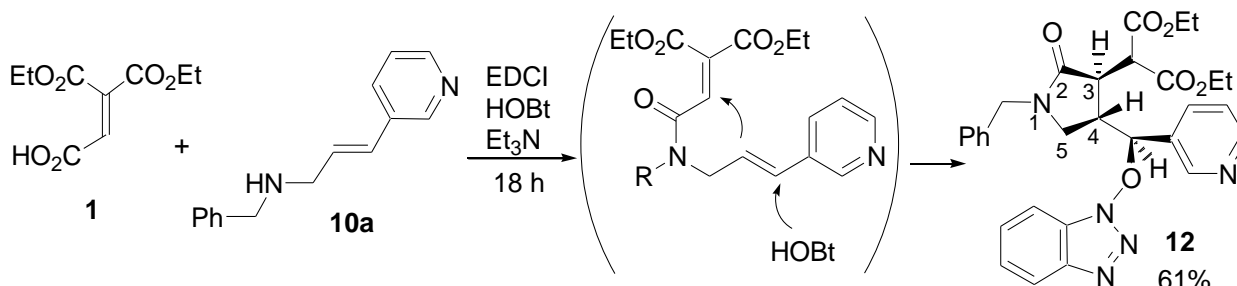
**Scheme 5-4.** The reaction of **1** and **10a**.

Understanding the detailed mechanism of the cycloadditions is important to find the factor

to control the selectivity. In order to explain the observed *cis*- and *trans*-fused selectivity, and

examine the applicability of the reaction models[10] on the selectivity to heteroaryl ring systems,

the reaction mechanism was investigated using B3LYP/6-31G*,[12,13] ωB97X-D[14] and M06-2X[15]

calculations including the PCM[16] solvent effect (solvent=THF). TS geometry was characterized

by vibrational analysis, which checked whether the obtained geometry has single imaginary

frequencies ($v^{\ddagger}$). From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC)

method[17] to obtain the energy-minimum geometries. ΔE (sum of electronic and zero-point

energies) were refined by single-point calculations of RB3LYP/6-311+G(d,p) SCRF = (PCM,

solvent = THF), RwB97X-D and RM06-2X/6-311+G(d,p) SCRF = (PCM, solvent = THF),

respectively.

The *cis* and *trans*-fused stereoselectivity for reaction of 3-(2- and 3-furyl)-2-propenyl-

amides in the [4 + 2] cycloaddition path has been examined. For 2-furan, the stepwise path to

trans-fused [4 + 2] cycloadduct and the concerted path to *cis*-fused [4 + 2] cycloadduct were

calculated by B3LYP functional (Scheme 5-5). On the other hand, the concerted paths to both

*trans*- and *cis*-fused [4 + 2] cycloadducts were obtained by ωB97X-D and M06-2X.

Although the calculation method dependency is seen, the activation energies TS2 for the paths leading to *trans* cycloadduct **3M-*trans*** are lower than those of TS3 for the paths leading to *cis*-[4 + 2] cycloadduct **3M-*cis***, but *trans*-[4 + 2] cycloadduct **3M-*trans*** is less stable than *cis*-[4 + 2] cycloadduct **3M-*cis*** in each calculation methods. The stability of **3M-*cis*** may be partially attributed to **3a,4a-*cis*** (1,3-diequatorial-like) conformation of the cyclohexene ring. At higher temperature, the reverse reaction may occur and the reaction leads to the more stable [4 + 2] cycloadduct **3M-*cis***.

For 3-furan, both concerted paths lead to *cis* and *trans* adducts by B3LYP, ωB97X-D and M06-2X functionals (Scheme 5-6). Similarly, the activation energy TS4 for the path leading to *trans* cycloadduct **6M-*trans*** are lower than TS5 for the path leading to *cis*-[4 + 2] cycloadduct **6M-*cis***, but *trans*-[4 + 2] cycloadduct **6M-*trans*** is less stable than *cis*-[4 + 2] cycloadduct **6M-*cis***.

The relative stability of **3M-*trans*** to the precursor **AM1** (ΔE^o = +1.59, [-14.16], -13.80 kcal/mol) is lower than that of **6M-*trans*** to **CM1** (ΔE^o = -4.31, [-17.77], -17.87 kcal/mol) within each calculation method. The bond length C4-C3a in **3M-*trans*** is longer than C8-C8a in **6M-*trans*** within each calculation method. The longer C4-C3a bond possibly arises from the larger zwitter-ionic character of **3M-*trans*** compared to **6M-*trans*** (Scheme 5-7). 2-Furylmethyl cation is 9.4 kcal/mol[18] more stable than 3-furylmethyl cation, possibly because of more effective delocalization of positive charge by contributions from resonance structures. Therefore, the reverse reaction of **6M-*trans*** ($\rightarrow$ **CM1**) may be less facile than that of **3M-*trans*** ($\rightarrow$ **AM1**). The path with the lower activation energy TS4 via *trans*-[4 + 2] cycloadduct **6M-*trans*** may give the final stable furan-reproduced product **7M-*trans*** by the stepwise protonation-deprotonation (1,3-H$^+$ shift) under the reaction conditions.
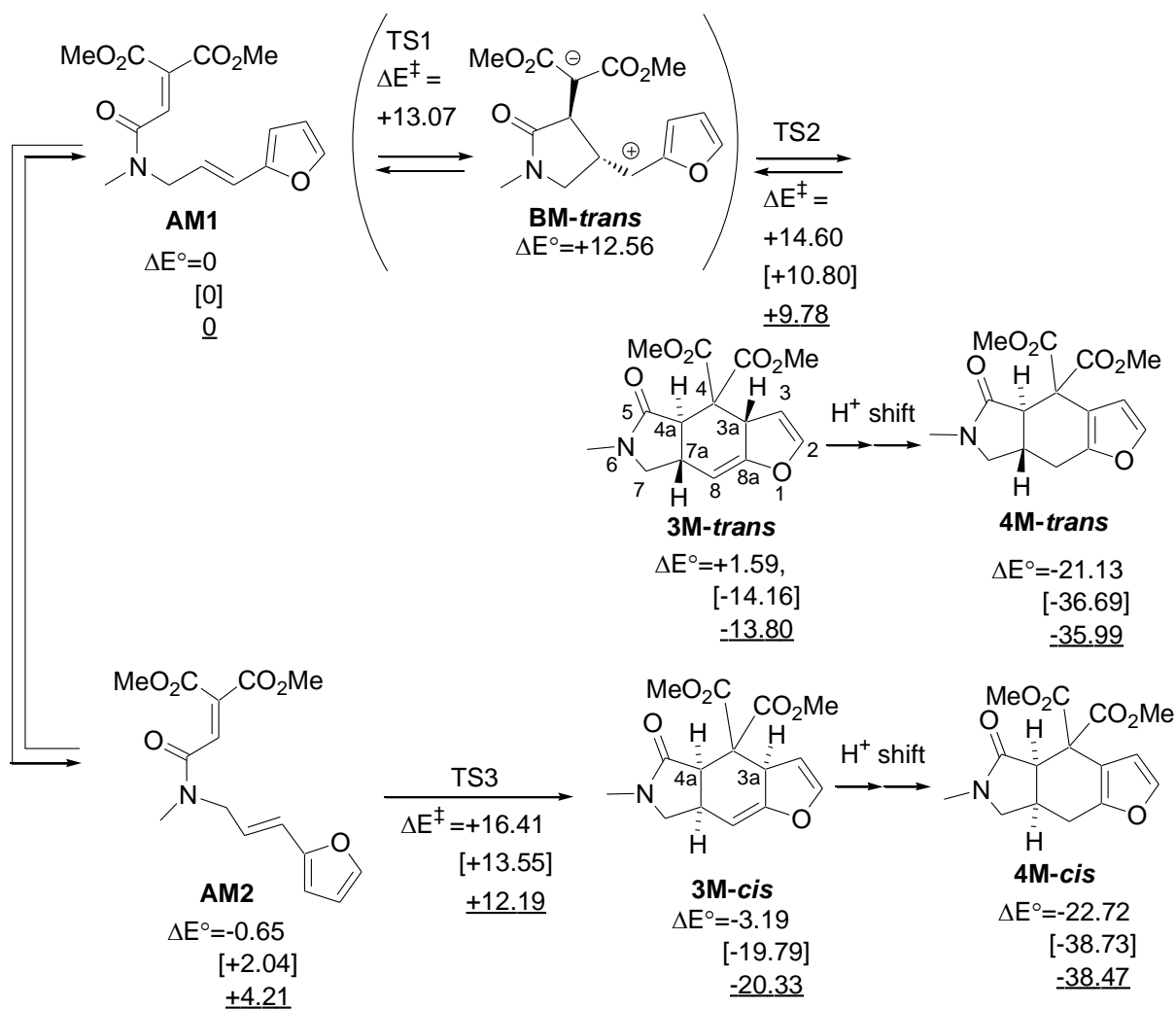
Scheme 5-5. [4 + 2] Cycloaddition path for (2-furyl)-2-propenylamide. ΔE's (sum of electronic and zero-point energies) by RB3LYP/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RB3LYP/6-31G* SCRF = (PCM, solvent = THF), RwB97XD/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RwB97XD /6-31G* SCRF = (PCM, solvent = THF) in square brackets [ ], and RM062X/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RM062X/6-31G* SCRF = (PCM, solvent = THF) with underline, relative to **AM1** are shown.
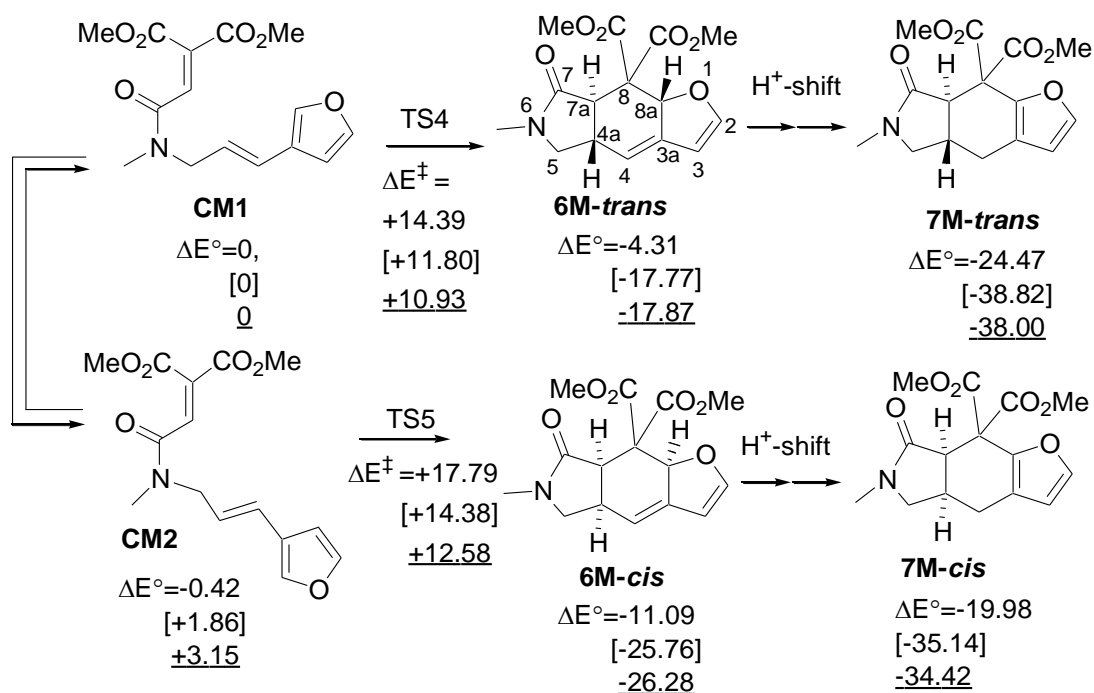
Scheme 5-6. [4 + 2] Cycloaddition path for (3-furyl)-2-propenylamide. ΔE's (sum of electronic and zero-point energies) by RB3LYP/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RB3LYP/6-31G* SCRF = (PCM, solvent = THF), RwB97XD/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RwB97XD /6-31G* SCRF = (PCM, solvent = THF) in square brackets [ ], and RM062X/6-311+G(d,p) SCRF = (PCM, solvent = THF) // RM062X/6-31G* SCRF = (PCM, solvent = THF) with underline, relative to **CM1** are shown.

	C4-C3a	C8-C8a
B3LYP	1.609 Å	1.593 Å
wB97XD	1.594 Å	1.582 Å
M062X	1.593 Å	1.580 Å
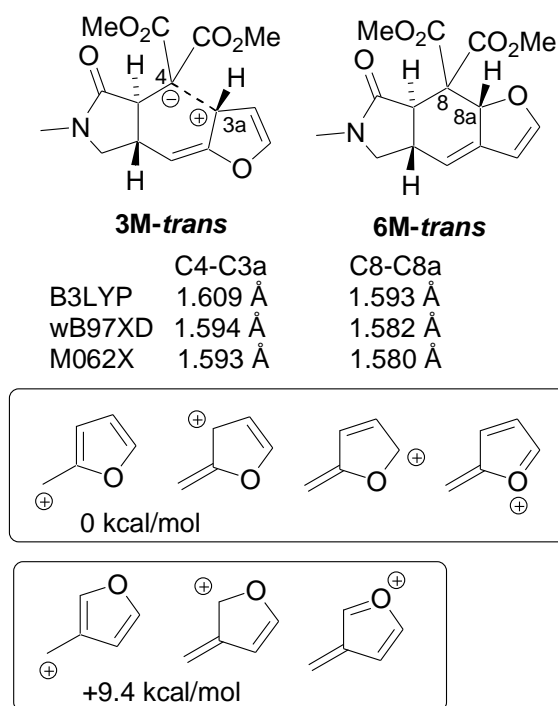
Scheme 5-7. Bond lengths C4-C3a (**3M-*trans***) and C8-C8a (**6M-*trans***) and resonance structures of 2- and 3-furylmthyl cations.

5-3 Conclusion

In summary, sequential reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with 3-heteroarylpropenylamines has been examined. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with *E*-3-(2-furyl)-2-propenylamines under the amide formation conditions gave *cis*-fused tricyclic compounds on heating, via the amide formation, [4 + 2] cycloaddition, and H-shift reactions. On the other hand, the reaction with *E*-3-(3-furyl)-2-propenylamines gave *trans*-fused tricyclic compounds. The origin of observed stereoselectivity of the fused rings has been examined by the DFT calculations. The difference between 2-furyl and 3-furyl derivatives in the stereoselectivity of the products may arise from the delocalization of positive charge of 2-furylmethyl and 3-furylmethyl cations. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with 3-(3-pyridinyl)-2-propen-1-amine under the amide formation conditions gave HOBt-incorporated 3,4-*trans*-pyrrolidine selectively. The scope and limitation under the reaction

conditions have been described. The results are useful for the study on the effects of various vinyl heteroarenes in the sequential reactions.

5-4 Experimental Section

General Procedures

[1]H Chemical shifts are reported in ppm relative to Me$_4$Si. [13]C Chemical shifts are reported in ppm relative to CDCl$_3$ (77.1 ppm). [13]C mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI. Mass analyzer type used for EI is double-focusing. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75-150 μm).

Ethenetricarboxylate **1** was prepared according to the literature.[19] *E*-3-heteroaryl-2- propenylamines **2a-b**, **5a-b**, were prepared from the corresponding *E*-3-heteroaryl-2-propenals and amines by reductive amination in methanol according to the literature procedure.[20] *E*-3-(2-furyl)-2-propenal, [21] *E*-3-(5-bromo-2-furyl)-2-propenal,[21] *E*-3-(3-furyl)-2-propenal, [22] *E*-3-(3-thienyl)-2-propenal, [23] *E*-3-(5-bromo-2-thienyl)-2-propenal, [24] *E*-3-(4-pyridinyl)-2-propenal, [25] and *E*-3-(3-pyridinyl)-2-propenal[25, 26] were prepared by the reaction of the corresponding heteroarylaldehydes and formylmethylenetriphenylphosphorane according to the literature procedure. *E*-3-(2-thienyl)-2-propenal was prepared according to the literature.[27]

2a: (8.9 mmol scale, 1.43 g, 75%); R$_f$ = 0.4 (hexane-ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.81 (bs, 1H), 3.38 (dd, *J* = 6.2, 1.3 Hz, 2H), 3.81 (s, 2H), 6.19 (d, *J* = 3.3 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.2 Hz, 1H), 6.33-6.39 (m, 2H), 7.22-7.27 (m, 1H), 7.29-7.33 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.74 (CH$_2$), 53.19 (CH$_2$), 107.22 (CH), 111.20 (CH), 119.90 (CH), 127.03 (CH), 127.14 (CH), 128.22 (CH), 128.46 (CH), 140.12 (C), 141.76 (CH), 152.73 (C); IR (neat) 3311, 3027, 2824, 1494, 1453, 1361, 1254, 1151, 1012 cm^{-1}; MS (EI) m/z 213 (M$^+$, 44), 122 (54), 91 (100%); HRMS (EI) m/z 213.1137 (calcd for C$_{14}$H$_{15}$NO 213.1154).

2b: (4.0 mmol scale, 640 mg, 54%); $R_f = 0.3$ (hexane-ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.57 (bs, 1H), 3.38 (d, $J = 4.7$ Hz, 1H), 3.81 (s, 2H), 6.13 (d, $J = 3.3$ Hz, 1H), 6.20-6.30 (m, 3H), 7.22-7.28 (m, 1H), 7.30-7.33 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.58 (CH$_2$), 53.26 (CH$_2$), 109.41 (CH), 112.94 (CH), 118.81 (CH), 121.14 (C), 127.06 (CH), 128.12 (CH), 128.19 (CH), 128.44 (CH), 128.48 (C), 140.22 (C), 154.79 (C); IR (neat) 3313, 3027, 2816, 1488, 1453, 1128, 1012 cm^{-1}; MS (EI) m/z 293 (M$^+$, 2.7), 291 (M$^+$, 2.7), 212 (47), 91 (100%); HRMS (EI) m/z 291.0263, 293.0241 (calcd for C$_{14}$H$_{14}$BrNO 291.0259, 293.0238).

5a: (1.6 mmol scale, 222 mg, 65%); $R_f = 0.3$ (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.52 (bs, 1H), 3.37 (dd, $J = 6.4$, 1.4 Hz, 2H), 3.81 (s, 2H), 6.03 (dt, $J = 15.8$, 6.4 Hz, 1H), 6.39 (bd, $J = 15.8$ Hz, 1H), 6.52 (dd, $J = 1.2$, 0.6 Hz, 1H), 7.23-7.28 (m, 1H), 7.30-7.36 (m, 5H), 7.38 (bs, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 51.18 (CH$_2$), 53.39 (CH$_2$), 107.64 (CH), 121.17 (CH), 124.04 (C), 127.03 (CH), 128.13 (CH), 128.22 (CH), 128.47 (CH), 140.11 (CH), 140.30 (C), 143.50 (CH); IR (neat) 3327, 3026, 2815, 1495, 1453, 1159, 1072, 1024 cm^{-1}; MS (EI) m/z 213 (M$^+$, 32), 184 (17), 122 (25), 91 (100%); HRMS (EI) m/z 213.1172 (calcd for C$_{14}$H$_{15}$NO 213.1154).

5b: (2.3 mmol scale, 230 mg, 43%); $R_f = 0.3$ (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.865-0.965 (m, 2H), 1.10-1.30 (m, 3H), 1.41-1.52 (m, 1H), 1.65-1.77 (m, 5H), 2.46 (d, $J = 6.6$ Hz, 2H), 3.33 (dd, $J = 6.4$, 1.4 Hz, 2H), 6.02 (dt, $J = 15.8$, 6.4 Hz, 1H), 6.37 (d, $J = 15.8$ Hz, 1H), 6.52 (d, $J = 1.6$ Hz, 1H), 7.34 (d, $J = 1.6$ Hz, 1H), 7.38 (bs, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 26.11 (CH$_2$), 26.72 (CH$_2$), 31.52 (CH$_2$), 38.13 (CH), 52.09 (CH$_2$), 56.34 (CH$_2$), 107.67 (CH), 120.80 (CH), 124.10 (C), 128.52 (CH), 140.01 (CH), 143.43 (CH); IR (neat) 3329, 2922, 1508, 1448, 1161, 1025 cm^{-1}; MS (EI) m/z 219 (M$^+$, 24), 136 (40), 107 (100%); HRMS (EI) m/z 219.1621 (calcd for C$_{14}$H$_{21}$NO 219.1623).

8a: (2.25 mmol scale, 396 mg, 77%); $R_f = 0.2$ (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.50 (bs, 1H), 3.39 (dd, $J = 6.3$, 1.5 Hz, 2H), 3.82 (s, 2H), 6.15 (dt, $J = 15.6$, 6.3 Hz, 1H), 6.67 (d, $J = 15.6$ Hz, 1H), 6.91 (d, $J = 3.6$ Hz, 1H), 6.94 (dd, $J = 5.0$, 3.6 Hz,

1H), 7.12 (d, J = 5.0 Hz, 1H), 7.23-7.29 (m, 1H), 7.31-7.35 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.96 (CH$_2$), 53.37 (CH$_2$), 123.94 (CH), 124.59 (CH), 125.20 (CH), 127.06 (CH), 127.34 (CH), 128.24 (CH), 128.32 (CH), 128.50 (CH), 140.25 (C), 142.37 (C); IR (neat) 3308, 3026, 2818, 1495, 1453, 1203, 1117 cm^{-1}; MS (EI) m/z 229 (M$^+$, 100), 138 (44), 132 (47%); HRMS (EI) m/z 229.0922 (calcd for C$_{14}$H$_{15}$NS 229.0925).

8b: (5.2 mmol scale, 1.29 g, 72%); R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.56 (bs, 1H), 3.35 (dd, J = 6.3, 1.6 Hz, 2H), 3.80 (s, 2H), 6.04 (dt, J = 15.6, 6.3 Hz, 1H), 6.54 (dtd, J = 15.6, 1.6, 0.5 Hz, 1H), 6.63 (d, J = 3.8 Hz, 1H), 6.87 (d, J = 3.8 Hz, 1H), 7.23-7.29 (m, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.77 (CH$_2$), 53.34 (CH$_2$), 110.59 (C), 124.04 (CH), 125.40 (CH), 127.08 (CH), 128.20 (CH), 128.49 (CH), 128.81 (CH), 130.17 (CH), 140.03 (C), 143.95 (C); IR (neat) 3311, 3026, 2819, 1643, 1494, 1453, 1436, 1361, 1197, 1118, 1051, 1028 cm^{-1}; MS (EI) m/z 309 (M$^+$, 20), 307 (M$^+$, 20), 228 (62), 132 (44), 91 (100%); HRMS (EI) m/z 307.0025, 309.0012 (calcd for C$_{14}$H$_{14}$BrNS 307.0030, 309.0010).

9: (0.44 mmol scale, 63 mg, 66%); R$_f$ = 0.2 (hexane-EtOAc = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.56 (bs, 1H), 3.39 (dd, J = 6.4, 1.4 Hz, 2H), 3.81 (s, 2H), 6.16 (dt, J = 15.8, 6.4 Hz, 1H), 6.54 (d, J = 15.8 Hz, 1H), 7.09 (bs, 1H), 7.19 (dd, J = 5.1, 1.4 Hz, 1H), 7.21-7.29 (m, 2H), 7.30-7.35 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 51.15 (CH$_2$), 53.33 (CH$_2$), 121.59 (CH), 125.02 (CH), 125.69 (CH), 125.99 (CH), 127.01 (CH), 128.21 (CH), 128.32 (CH), 128.46 (CH), 139.77 (C), 140.22 (C); IR (neat) 3313, 3025, 2817, 1494, 1453, 1118 cm^{-1}; MS (EI) m/z 229 (M$^+$, 36), 132 (56), 91 (100%); HRMS (EI) m/z 229.0925 (calcd for C$_{14}$H$_{15}$NS 229.0925).

10a: (2.9 mmol scale, 193 mg, 29%); R$_f$ = 0.2 (ether-MeOH = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.89 (bs, 1H), 3.46 (dd, J = 6.1, 1.0 Hz, 2H), 3.84 (s, 2H), 6.38 (dt, J = 16.0, 6.1 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 7.21 (dd, J = 7.9, 4.8 Hz, 1H), 7.24-7.29 (m, 1H), 7.31-7.36 (m, 4H), 7.67 (ddd, J = 7.9, 2.0, 1.4 Hz, 1H), 8.44 (dd, J = 4.7, 1.4 Hz, 1H), 8.57 (d, J =

2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 51.05 (CH$_2$), 53.42 (CH$_2$), 123.43 (CH), 127.09 (CH), 127.68 (CH), 128.19 (CH), 128.48 (CH), 130.94 (CH), 132.69 (CH), 132.72 (C), 140.02 (C), 148.22 (CH), 148.42 (CH); IR (neat) 3296, 3027, 2822, 1651, 1568, 1453, 1415, 1122, 1025 cm^{-1}; MS (EI) m/z 224 (M$^+$, 5.7), 132 (20), 118 (23), 91 (100%); HRMS (EI) m/z 224.1319 (calcd for C$_{15}$H$_{16}$N$_2$ 224.1313).

10b: (1.6 mmol scale, 112 mg, 31%); R$_f$ = 0.4 (ether-MeOH = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.76 (bs, 1H), 3.47 (d, J = 4.7 Hz, 2H), 3.84 (s, 2H), 6.51 (d, J = 15.9 Hz, 1H), 6.52 (dt, J = 15.9, 4.7 Hz, 1H), 7.21-7.22 (m, 2H), 7.24-7.35 (m, 5H), 8.51-8.52 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 50.85 (CH$_2$), 53.51 (CH$_2$), 120.85 (CH), 127.15 (CH), 128.20 (CH), 128.53 (CH), 128.82 (CH), 133.73 (CH), 140.02 (C), 144.52 (C), 150.13 (CH); IR (neat) 3295, 3026, 2923, 1650, 1597, 1550, 1494, 1453, 1415 cm^{-1}; MS (EI) m/z 224 (M$^+$, 17), 132 (25), 91 (100%); HRMS (EI) m/z 224.1315 (calcd for C$_{15}$H$_{16}$N$_2$ 224.1313).

Typical experimental procedure for preparation of 3, 4, 6, 7, 11, 12 (Table 5-1, entry 3). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF$_3$CO$_2$H (4 mL)) in benzene (0.7 mL) were added **2a** (213 mg, 1 mmol) in benzene (0.7 mL), Et$_3$N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol), and EDCI (1-[3-(dimethyl-amino)propyl]- 3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to 80 °C and stirred for 20 h. The reaction mixture was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2 M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **3a** (252 mg, ca. 61%).

3a,b and **6** are unstable and decompose to give complex mixtures gradually. **3a,b** are freshly prepared and used immediately in Table 5-2.

3a: R_f = 0.5 (hexane-ether = 1 : 8); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.18 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.98-3.03 (m, 1H), 3.22-3.24 (m, 2H), 3.37-3.42 (m, 1H), 4.01 (d, J = 14.7 Hz, 1H), 4.01-4.21 (m, 3H), 4.28-4.53 (m, 2H), 4.92 (d, J = 14.7 Hz, 1H), 4.97-4.98 (m, 1H), 5.32-5.33 (m, 1H), 6.45 (dd, J = 2.9, 2.3 Hz, 1H), 7.25-7.35 (m, 5H). Selected NOEs are between δ 3.22-3.24 (C5a-*H*,8a-*H* (overlapped)) and δ 3.37-3.42 (C8-H*H*), 4.01-4.21 (C3a-*H* (overlapped)), 4.97-4.98 (C9-*H*) and between δ 4.97-4.98 (C9-*H*) and δ 2.98-3.03 (C8-*H*H), 3.37-3.42 (C8-H*H*). Atom numbering is shown in Table 5-1.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.92 (CH$_3$), 14.10 (CH$_3$), 31.09 (CH), 47.16 (CH$_2$), 48.16 (CH), 49.92 (CH), 51.76 (CH$_2$), 58.32 (C), 61.30 (CH$_2$), 62.42 (CH$_2$), 95.51 (CH), 104.53 (CH), 127.51 (CH), 128.48 (CH), 128.59 (CH), 136.61 (C), 144.49 (CH), 155.79 (C), 167.70 (C), 170.24 (C), 172.19 (C). Selected HMBC correlations are between δ 2.98-3.03 (C8-*H*H), 3.22-3.24 (C5a-*H*,8a-*H* (overlapped)) and δ 95.51 (*C*9), δ 3.22-3.24 (C5a-*H*,8a-*H* (overlapped)) and δ 51.76 (*C*8), and between δ 3.37-3.42 (C8-H*H*) and δ 48.16 (*C*5a).

3b: (Table 5-1, entry 9, 1.0 mmol scale, 361 mg, ca. 73%); R_f = 0.5 (hexane-ether = 1 : 8); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.21 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.97-3.04 (m, 1H), 3.17-3.25 (m, 2H), 3.37-3.41 (m, 1H), 4.01 (d, J = 14.7 Hz, 1H), 4.01-4.11 (m, 2H), 4.20 (dq, J = 10.7, 7.1 Hz, 1H), 4.27-4.44 (m, 2H), 4.92 (d, J = 14.7 Hz, 1H), 5.05-5.06 (m, 1H), 5.35 (dd, J = 2.5, 1.0 Hz, 1H), 7.24-7.34 (m, 5H). Selected NOEs are between δ 3.17-3.25 (C5a-*H*,8a-*H* (overlapped)) and δ 3.37-3.41 (C8-H*H*), 4.01-4.11 (C3a-*H* (overlapped)), 5.05-5.06 (C9-*H*) and between δ 5.05-5.06 (C9-*H*) and δ 2.97-3.04 (C8-*H*H), 3.37-3.41 (C8-H*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.90 (CH$_3$), 14.05 (CH$_3$), 30.55 (CH), 47.14 (CH$_2$), 47.78 (CH), 51.18 (CH), 51.44 (CH$_2$), 58.33 (C), 61.37 (CH$_2$), 62.53 (CH$_2$), 97.12 (CH), 105.00 (CH), 127.50 (CH), 128.42 (CH), 128.55 (CH), 129.04 (C), 136.42 (C), 154.89 (C), 167.39 (C), 169.75 (C), 171.76 (C).

Transformation of 3a to 4a (Table 5-2, entry 1): To a solution of **3a** (252 mg, 0.62 mmol) in ClCH$_2$CH$_2$Cl (1.0 mL) was added 1M HCl/Ether (0.62 mL, 0.62 mmol) and H$_2$O (9 mg, 0.5 mmol). The mixture was stirred at 80 °C for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane-Et$_2$O to give **4a** (139 mg, 78%).

4a: R$_f$ = 0.7 (hexane-ether = 1 : 8); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.21 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 2.23 (dd, J = 17.2, 8.2 Hz, 1H), 2.76 (dd, J = 17.2, 8.2 Hz, 1H), 2.86 (d, J = 9.6 Hz, 1H), 3.18 (dddd, J = 8.2, 8.2, 6.3, 4.5 Hz, 1H), 3.51 (dd, J = 9.6, 4.5 Hz, 1H), 3.69 (d, J = 6.3 Hz, 1H), 4.05-4.21 (m, 2H), 4.20 (d, J = 14.7 Hz, 1H), 4.28-4.50 (m, 2H), 4.60 (d, J = 14.7 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 7.16-7.19 (m, 2H), 7.26 (d, J = 2.0 Hz, 1H), 7.27-7.34 (m, 3H). Selected NOEs are between δ 3.18 (C7a-*H*) and δ 3.69 (C4a-*H*), 3.51 (C7-H*H*), 2.76 (C8-H*H*) and between δ 3.69 (C4a-*H*) and δ 3.51 (C7-H*H*). Atom numbering is shown in Table 5-1.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.94 (CH$_3$), 14.09 (CH$_3$), 24.68 (CH$_2$), 31.33 (CH), 46.89 (CH$_2$), 47.18 (CH), 51.57 (CH$_2$), 53.99 (C), 61.71 (CH$_2$), 62.00 (CH$_2$), 111.93 (CH), 113.08 (C), 127.82 (CH), 128.51 (CH), 128.81 (CH), 136.14 (C), 140.86 (CH), 149.82 (C), 168.74 (C), 169.81 (C), 171.00 (C). Selected HMBC correlations are between δ 2.23 (C8-*H*H), 2.76 (C8-H*H*), 2.86 (C7-*H*H), 3.69 (C4a-*H*) and δ 31.33 (*C*7a), δ 2.86 (C7-*H*H), 3.69 (C4a-*H*) and δ 24.68 (*C*8), and between δ 3.69 (C4a-*H*) and δ 53.99 (*C*4).; IR (neat) 2981, 1732, 1513, 1443, 1366, 1243, 1147, 1109, 1038 cm^{-1}; MS (EI) m/z 411 (M$^+$, 10), 322 (14), 248 (33), 204 (42), 84 (100%); HRMS (EI) m/z 411.1691 (calcd for C$_{23}$H$_{25}$NO$_6$ 411.1662).

4b: (Table 5-2, entry 2, 0.39 mmol scale, 143 mg, 74%); R$_f$ = 0.7 (hexane-ether = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.19 (dd, J = 17.4, 8.2 Hz, 1H), 2.74 (dd, J = 17.4, 8.2 Hz, 1H), 2.86 (d, J = 9.8 Hz, 1H), 3.18 (dddd, J = 8.2, 8.2, 6.1, 4.4 Hz, 1H), 3.51 (dd, J = 9.8, 4.4 Hz, 1H), 3.67 (d, J = 6.1 Hz, 1H), 4.03-4.46 (m, 4H), 4.17 (d, J = 14.7 Hz, 1H), 4.62 (d, J = 14.7 Hz, 1H), 6.67 (s, 1H), 7.17-7.19 (m, 2H), 7.28-7.35 (m, 3H). Selected NOEs are between δ 3.18 (C7a-*H*) and δ 3.67 (C4a-*H*), 3.51

(C7-H*H*), 2.74 (C8-H*H*) and between δ 3.67 (C4a-*H*) and δ 3.51 (C7-H*H*).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.94 (CH$_3$), 14.07 (CH$_3$), 24.47 (CH$_2$), 31.06 (CH), 46.89 (CH$_2$), 46.96 (CH), 51.47 (CH$_2$), 53.79 (C), 61.93 (CH$_2$), 62.26 (CH$_2$), 113.39 (CH), 115.80 (C), 120.51 (C), 127.90 (CH), 128.50 (CH), 128.86 (CH), 135.98 (C), 151.48 (C), 168.28 (C), 169.25 (C), 170.73 (C). Selected HMBC correlations are between δ 2.19 (C8-*H*H), 2.74 (C8-H*H*), 2.86 (C7-*H*H), 3.67 (C4a-*H*) and δ 31.06 (*C*7a), δ 2.86 (C7-*H*H), 3.51 (C7-H*H*), 3.67 (C4a-*H*) and δ 24.47 (*C*8), and between δ 3.67 (C4a-*H*) and δ 53.79 (*C*4).; IR (neat) 2981, 1738, 1697, 1516, 1443, 1366, 1293, 1246, 1194, 1045, 1029 cm^{-1}; MS (EI) m/z 491 (M$^+$, 40), 489 (39), 418 (19), 416 (19), 372 (38), 370 (36), 91 (100%); HRMS (EI) m/z 489.0797, 491.0782 (calcd for C$_{23}$H$_{24}$BrNO$_6$ 489.0787, 491.0767).

6a: (0.93 mmol scale, 227 mg, ca. 59%); R$_f$ = 0.5 (ether = 1 : 8); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.29 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.60-2.69 (m, 1H), 2.83 (d, *J* = 12.3 Hz, 1H), 3.09 (dd, *J* = 10.2, 9.1 Hz, 1H), 3.44 (dd, *J* = 9.1, 7.7 Hz, 1H), 4.21-4.41 (m, 5H), 4.53 (d, *J* = 14.8 Hz, 1H), 5.31 (dd, *J* = 3.9, 2.9 Hz, 1H), 5.68-5.70 (m, 2H), 6.81 (d-like, *J* = 2.5 Hz, 1H), 7.21-7.35 (m, 5H). Selected NOEs are between δ 2.60-2.69 (C4a-*H*) and δ 5.68-5.70 (C4-*H* (overlapped)), 5.31 (C8a-*H*), 3.44 (C5-H*H*), and between δ 3.09 (C5-*H*H) and δ 5.68-5.70 (C4-*H* (overlapped)). Atom numbering is shown in Table 5-3.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.09 (CH$_3$), 14.13 (CH$_3$), 36.46 (CH), 46.82 (CH$_2$), 48.20 (CH$_2$), 52.51 (CH), 56.38 (C), 62.17 (CH$_2$), 62.21 (CH$_2$), 84.48 (CH), 104.38 (CH), 112.49 (CH), 127.60 (CH), 128.16 (CH), 128.74 (CH), 136.64 (C), 143.30 (C), 154.35 (CH), 167.43 (C), 169.48 (C), 170.45 (C). Selected HMBC correlations are between δ 3.09 (C5-*H*H), 3.44 (C5-H*H*), and δ 36.46 (*C*4a), δ 3.44 (C5-H*H*) and δ 52.51 (*C*7a), δ 3.44 (C5-H*H*), 2.83 (C7a-*H*), and δ 112.49 (*C*4), and between δ 2.83 (C7a-*H*) and δ 56.38 (*C*8).

7a: (Table 5-2, entry 2, 1.0 mmol scale, 321 mg, 78%); R$_f$ = 0.5 (hexane-ether = 1 : 8) ; pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.28 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 H, 3H), 2.39 (dd, *J* = 14.8, 10.6 Hz, 1H), 2.59 (ddddd, *J* = 12.5, 10.6, 9.0, 7.4, 4.9 Hz, 1H), 2.66 (dd, *J* =

14.8, 4.9 Hz, 1H), 3.03 (dd, J = 9.2, 9.0 Hz, 1H), 3.07 (d, J = 12.5 Hz, 1H), 3.39 (dd, J = 9.2, 7.4 Hz, 1H), 4.13-4.21 (m, 1H), 4.31-4.40 (m, 4H), 4.62 (d, J = 14.7 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 7.21-7.36 (m, 5H), 7.38 (d, J = 2.0 Hz, 1H). Selected NOEs are between δ 2.59 (C4a-H) and δ 3.39 (C5-HH) and between δ 3.03 (C5-HH), 3.07 (C7a-H) and δ 2.39 (C4-HH). Atom numbering is shown in Table 5-3.; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.07 (CH$_3$), 14.09 (CH$_3$), 25.72 (CH$_2$), 34.10 (CH), 46.58 (CH$_2$), 49.72 (CH$_2$), 51.86 (CH), 57.09 (C), 61.97 (CH$_2$), 62.73 (CH$_2$), 110.31 (CH), 120.77 (C), 127.58 (CH), 128.20 (CH), 128.73 (CH), 136.63 (C), 143.65 (CH), 145.66 (C), 167.09 (C), 168.26 (C), 171.00 (C). Selected HMBC correlations are between δ 2.39 (C4-HH), 2.66 (C4-HH), 3.39 (C5-HH), 3.07 (C7a-H), and δ 34.10 (C4a), δ 3.39 (C5-HH), 2.59 (C4a-H), and δ 51.86 (C7a), and between δ 3.07 (C7a-H) and δ 57.09 (C8).; IR (neat) 2982, 2937, 1739, 1497, 1443, 1367, 1256, 1193, 1148, 1039 cm^{-1}; MS (EI) m/z 411 (M$^+$, 14), 293 (14), 119 (58), 84 (100%); HRMS (EI) m/z 411.1696 (calcd for C$_{23}$H$_{25}$NO$_6$ 411.1682).

7b: (Table 5-2, entry 7, 1.0 mmol scale, 200 mg, 48%); R$_f$ = 0.6 (hexane-ether = 1 : 8) ; pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.919-1.01 (m, 2H), 1.13-1.23 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.60-1.68 (m, 3H), 1.71-1.74 (m, 3H), 2.44 (dd, J = 15.0, 11.0 Hz, 1H), 2.61 (ddddd, J = 12.7, 11.0, 9.4, 7.5, 4.9 Hz, 1H), 2.71 (dd, J = 15.0, 4.9 Hz, 1H), 3.04 (d, J = 12.7 Hz, 1H), 3.06 (dd, J = 13.6, 7.2 Hz, 1H), 3.16 (dd, J = 9.4, 9.1 Hz, 1H), 3.21 (dd, J = 13.6, 7.4 Hz, 1H), 3.53 (dd, J = 9.1, 7.5 Hz, 1H), 4.15 (dq, J = 10.7, 7.1 Hz, 1H), 4.26-4.41 (m, 3H), 6.24 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H). Selected NOEs are between δ 2.61 (C4a-H) and δ 3.53 (C5-HH), between δ 3.16 (C5-HH), 3.04 (C7a-H) and δ 2.44 (C4-HH).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.02 (CH$_3$), 14.07 (CH$_3$), 25.82 (CH$_2$), 25.85 (CH$_2$), 25.87 (CH$_2$), 26.45 (CH$_2$), 30.87 (CH$_2$), 30.90 (CH$_2$), 34.18 (CH), 36.24 (CH), 49.20 (CH$_2$), 51.31 (CH$_2$), 51.92 (CH), 57.03 (C), 61.85 (CH$_2$), 62.63 (CH$_2$), 110.30 (CH), 120.68 (C), 143.59 (CH), 145.88 (C), 167.07 (C), 168.24 (C), 171.07 (C). Selected HMBC correlations are between δ 2.44 (C4-HH), 2.71 (C4-HH), 3.53 (C5-HH), 3.04 (C7a-H), and δ 34.18 (C4a), δ 3.53 (C5-HH), 2.61 (C4a-H), and δ 51.92 (C7a), and between δ 3.04 (C7a-H) and δ 57.03 (C8).; IR

(neat) 2929, 2851, 1747, 1699, 1498, 1446, 1367, 1263, 1193, 1036 cm^{-1}; MS (EI) m/z 417 (M$^+$, 34), 335 (91), 59 (100%); HRMS (EI) m/z 417.2149 (calcd for $C_{23}H_{31}NO_6$ 417.2151).

11: (0.5 mmol scale, 118 mg, 45%); R_f = 0.7 (hexane-EtOAc = 1 : 1); red oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.22 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 3.46 (dd, J = 9.9, 5.9 Hz, 1H), 3.62 (dd, J = 6.5, 5.9 Hz, 1H), 3.70 (d, J = 9.9 Hz, 1H), 4.05-4.13 (m, 1H), 4.07 (d, J = 6.5 Hz, 1H), 4.20-4.28 (m, 1H), 4.32-4.49 (m, 4H), 7.05-7.07 (m, 2H), 7.26-7.32 (m, 3H), 7.82 (s, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.83 (CH$_3$), 13.99 (CH$_3$), 43.34 (CH), 46.86 (CH$_2$), 48.03, 48.05 (CH$_2$, CH), 55.54 (C), 62.48 (CH$_2$), 63.03 (CH$_2$), 125.30 (C), 127.88 (CH), 127.99 (CH), 128.76 (CH), 134.64 (CH), 135.51 (C), 139.54 (C), 143.88 (C), 166.81 (C), 167.46 (C), 170.05 (C), 188.11 (C); ^{1}H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.726 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 2.71 (dd, J = 9.8, 5.9 Hz, 1H), 3.46 (dd, J = 6.8, 5.9 Hz, 1H), 3.51(d, J = 9.8 Hz, 1H), 3.60 (dq, J = 10.6, 7.1 Hz, 1H), 3.84 (dq, J = 10.6, 7.1 Hz, 1H), 3.88 (d, J = 14.7 Hz, 1H), 3.99 (d, J = 6.8 Hz, 1H), 4.10 (d, J = 14.7 Hz, 1H), 4.30-4.38 (m, 2H), 6.83-6.86 (m, 2H), 6.99-7.10 (m, 3H), 8.13 (s, 1H). Selected NOEs are between δ 3.46 (C7a-H) and δ 3.99 (C4a-H), 2.71 (C7-HH), and between δ 3.99 (C4a-H) and δ 2.71 (C7-HH). Atom numbering is shown in Scheme 5-3.; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 13.56 (CH$_3$), 13.95 (CH$_3$), 43.74 (CH), 46.66 (CH$_2$), 47.72 (CH$_2$), 48.43 (CH), 56.15 (C), 62.42 (CH$_2$), 62.73 (CH$_2$), 124.92 (C), 127.88 (CH), 128.11 (CH), 128.79 (CH), 135.06 (CH), 136.13 (C), 140.32 (C), 144.42 (C), 166.76 (C), 167.91 (C), 169.73 (C), 187.97 (C). Selected HMBC correlations are between δ 3.99 (C4a-H) and δ 56.15 (*C*4), δ 2.71 (C7-HH), 3.51 (C7-HH), 3.46 (C7a-H) , 3.99 (C4a-H) and δ 187.97 (*C*8), and between δ 3.51 (C7-HH), 3.99 (C4a-H) and δ 43.74 (*C*7a).; IR (neat) 2981, 1738, 1699, 1667, 1409, 1258, 1229, 1195, 1095, 1016 cm^{-1}; MS (EI) m/z 521 (M$^+$, 25), 519 (M$^+$, 24), 402 (12), 401 (11), 119 (15), 118 (14), 91 (100%); HRMS (EI) m/z 519.0342, 521.0331 (calcd for $C_{23}H_{22}BrNO_6S$ 519.0351, 521.0331).

12: (0.75 mmol scale, 256 mg, 61%); R_f = 0.3 (ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.24 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 3.29 (dddd, J = 9.0, 7.0, 6.1, 5.5

Hz, 1H), 3.39 (dd, J = 7.0, 4.1 Hz, 1H), 3.60 (dd, J = 10.2, 9.0 Hz, 1H), 3.84 (d, J = 4.1 Hz, 1H), 3.87 (dd, J = 10.2, 5.5 Hz, 1H), 4.07-4.26 (m, 4H), 4.54 (d, J = 14.8 Hz, 1H), 4.63 (d, J = 14.8 Hz, 1H), 5.76 (d, J = 6.1 Hz, 1H), 7.14 (ddd, J = 8.2, 1.0, 1.0 Hz, 1H), 7.22-7.39 (m, 8H), 7.69 (ddd, J = 8.0, 2.0, 1.6 Hz, 1H), 7.90 (ddd, J = 8.3, 0.9, 0.9 Hz, 1H), 8.54 (dd, J = 4.9, 1.6 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H). Selected NOEs are between δ 3.39 (C3-H), 3.87 (C5-HH), 3.29 (C4-H) and δ 5.76 (CH(-3-Pyr)O) and between δ 3.29 (C4-H) and δ 3.84 (CH(CO$_2$Et)$_2$), 3.60 (C5-HH).; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.96 (CH$_3$), 13.99 (CH$_3$), 39.25 (CH), 44.32 (CH), 46.38 (CH$_2$), 47.00 (CH$_2$), 51.24 (CH), 61.91 (CH$_2$), 62.07 (CH$_2$), 91.01 (CH), 108.36 (CH), 120.28 (CH), 123.62 (CH), 124.66 (CH), 127.45 (C), 127.80 (CH), 128.18 (CH), 128.32 (CH), 128.81 (CH), 131.60 (C), 135.27 (CH), 135.72 (C), 143.21 (C), 148.65 (CH), 150.96 (CH), 167.63 (C), 168.30 (C), 171.67 (C). Selected HMBC correlations are between δ 3.60 (C5-HH), 3.87 (C5-HH), 3.39 (C3-H) and δ 171.67 (*C*2), between δ 3.60 (C5-HH), 3.87 (C5-HH), 3.39 (C3-H) and δ 39.25 (*C*4), and between δ 3.60 (C5-HH), 3.87 (C5-HH) and δ 91.01 (*C*H(-3-Pyr)O).; IR (KBr) 2982, 1734, 1696, 1592, 1496, 1445, 1372, 1259, 1177, 1027 cm^{-1}; MS (EI) m/z 557 (M$^+$, 2.5), 512 (2.5), 423 (68), 91 (100%); HRMS (EI) m/z 557.2264 (calcd for C$_{30}$H$_{31}$N$_5$O$_6$ 557.2274).

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Chapter 6

Intramolecular Cyclization Reactions of *β*-Substituted Cinnamylamides of Ethenetricarboxylate

6-1 Introduction

The development of atom-economical and efficient synthetic reactions which proceed under mild conditions is the continuing aim of organic chemistry. In this regard, intramolecular reactions of highly electrophilic ethenetricarboxylate with high chemo- and stereoselectivity are particularly attractive in view of their wide applicability for various synthetic reactions.

The alkyl substituents at alkene positions for the esters or amides have been studied by Snider and Roush[1] and by Yamazaki group work.[2] Lewis acid-promoted reactions of these substrates (Scheme 6-1) gave halogen or OH-incorporated five-membered rings, intramolecular ene adducts and also six-membered rings from 2-alkyl or aryl substituted (R^1) propenyl ester or amides of ethenetricarboxylate. In addition, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and 2-furylmethylamines in the presence of EDCI/HOBt/Et₃N at room temperature led directly to intramolecular Diels-Alder adducts, in chapter 2.[3]

The reaction of ethenetricarboxylates bearing aryl-substituted alkenyl groups as an extension of the alkene moiety was examined in chapters 3 and 4. In chapter 3, sequential intramolecular reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** with *E*-cinnamylamines **2** under the amide formation conditions led to pyrrolidine products in one pot, via intramolecular [2 + 2], [4 + 2] (IMDA) and some other cyclizations.[4] The types of the products depend on the substituents on benzene ring and the reaction conditions. Furthermore, the reaction of **1** with *Z*-cinnamylamines on heating gave [4 + 2] cycloadducts, *cis*-fused tricyclic compounds as the major products in chapter 4.[6] Reaction of **1** with 3,3-diaryl-2-propen-1-amines gave *cis*- and *trans*-fused tricyclic compounds selectively, depending on the substituents on the benzene ring, reaction temperature and solvent.
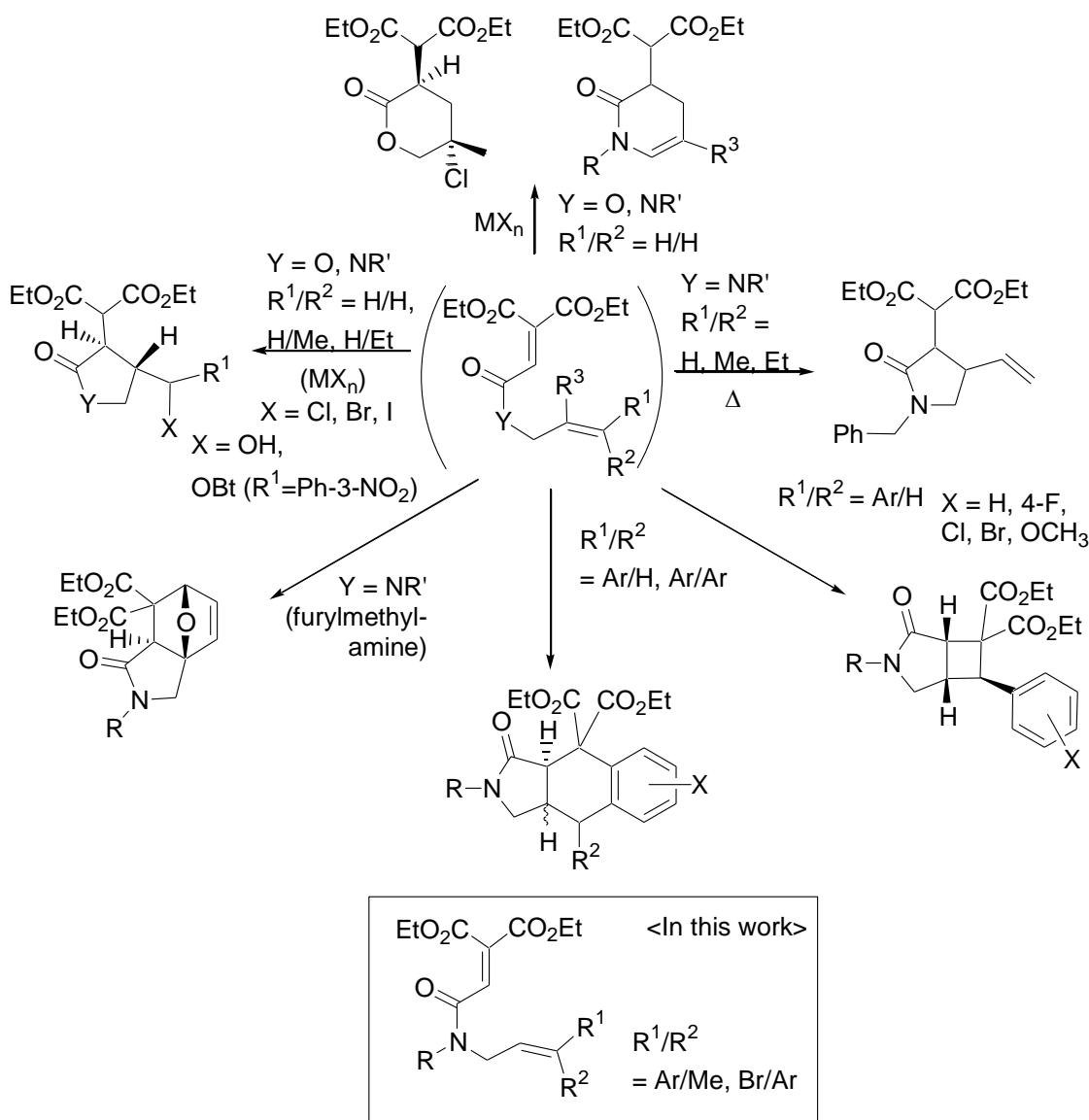
Scheme 6-1. The reaction of the esters and amides of ethenetricarboxylates.

To extend the scope of [2 + 2] and [4 + 2] cycloadditions of the cinnamyl derivatives and also to gain an insight into the mechanisms determining the chemoselectivity of four-membered and six-membered-ring formations, and other five-membered ring cyclization, the reactions of β-alkyl (Me) and halogen substituted cinnamyl derivatives have been examined in this study. The effects on benzene ring to selectivity of [2 + 2] and [4 + 2] cycloadditions have also been examined.

6-2 Results and Discussion

First, reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and (*E*)-*N*-benzyl-3-phenyl-2-buten-1-amine **2a** in the presence of EDCI/HOBt/Et$_3$N have been examined (Scheme 6-2). The reaction in THF gave cyclobutane-fused pyrrolidines **3a** in 22% yield as the isolable major product. The reaction in DMF gave **3a** in a better yield (49%). The relative configuration of **3a** was determined as shown in Scheme 6-2 by NOESY experiment. The intermediate amide, [4 + 2] cycloadducts and possible ene adducts were not observed under the reaction conditions. The reaction of **1** and **2a** at higher temperature (80-110 ºC) in benzene and toluene gave a complex mixture. The reaction of **1** and (*E*)-*N*-benzyl-3-*p*-tolyl-2-buten-1-amine (**2b**) at room temperature gave a mixture possibly containing cyclobutane-fused pyrrolidine but the products could not be purified. The reaction of **1** and **2b** at 110 ºC in toluene and DMF gave a complex mixture.
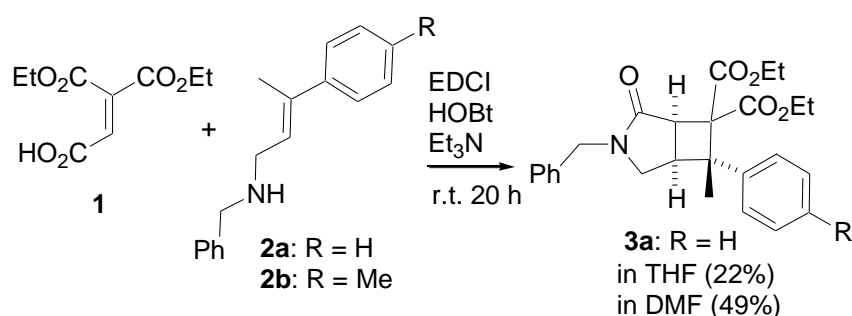
Scheme 6-2. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and (*E*)-*N*-benzyl -3-aryl-2-buten-1-amine **2**.

Next, the reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and cinnamylamines bearing electron-withdrawing groups in the presence of the amide condensation reagents was examined. Reaction of **1** and (*E*)-3-(4-(trifluoromethyl)phenyl)-2-buten-1-amine **2c** with EDCI/HOBt/Et$_3$N at room temperature and 110 °C in THF and DMF gave tetrahydrobenz[*f*]isoindoline **4c-aq** (axial methyl substituent) as the major product via [4 + 2]

cycloaddition (Table 6-1). The reaction of **1** and **2c** at 110 ºC in toluene gave a complex mixture. The stereochemistry of **4c-aq** was determined by NOEs.

The *trans*-fused tetrahydrobenz[*f*]isoindoline **4c-aq** may be formed via amide formation, IMDA reaction and H-transfer, similar to the reaction of *E*-cinnamylamines. Selective formation of the stereochemistry at the 4-methyl group may arise from the protonation from less hindered side (*cis* to adjacent H), similar to the reaction of 3,3-diaryl-2-propen-1-amines.

On the other hand, reaction of **1** and (*E*)-3-(4-nitrophenyl)-2-buten-1-amine **2d** with EDCI/HOBt/Et$_3$N at room temperature and 110 °C in DMF and toluene gave tetrahydrobenz[*f*]isoindoline **4d-eq** with the 4-methyl group *trans* to adjacent H as the major isolable product. Epimerization at C4 of the stereoisomer with 4-methyl *cis* to adjacent H initially formed (axial methyl substituent) would possibly provide the more stable **4d-eq** (equatrial methyl substituent). Related epimerization at C4 of tetrahydrobenz[*f*]isoindoline, using KOH in butanol or DMSO was reported by Oppolzer et al. [5,6]

Table 6-1. Reaction of (*E*)-3-aryl-2-buten-1-amines bearing electronwithdrawing groups **2c,d**.
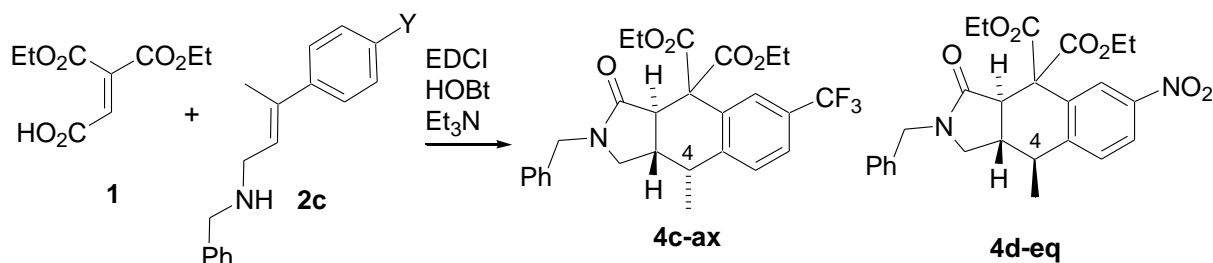
Entry	2	Y	Solvent	Temp.	Product	Yield(%)
1	**2c**	4-CF$_3$	THF	r.t.	**4c-ax**	60
2	**2c**	4-CF$_3$	DMF	r.t.	**4c-ax**	73
4	**2c**	4-CF$_3$	DMF	110 °C	**4c-ax**	58
6	**2d**	4-NO$_2$	DMF	r.t.	**4d-eq**	24
7	**2d**	4-NO$_2$	Toluene	110 °C	**4d-eq**	ca. 60[a]

[a] Including a small amount of possible stereoisomer.

Reaction of **1** and (*E*)-3-(3-nitrophenyl)-2-buten-1-amine **2e** with EDCI/HOBt/Et₃N at room temperature and 110 °C gave HOBt-incorporated 3,4-*trans*-pyrrolidine **5** as a single diastereomer in 40-85% yields (Scheme 6-3), in analogy to the reaction of *m*-nitrocinnamylamines and also 3-(3-pyridinyl)-2-propenylamine. The stereochemistry of **5** was deduced as shown in Scheme 6-3, similar to the proposed mechanism for formation of those HOBt adducts.[4]
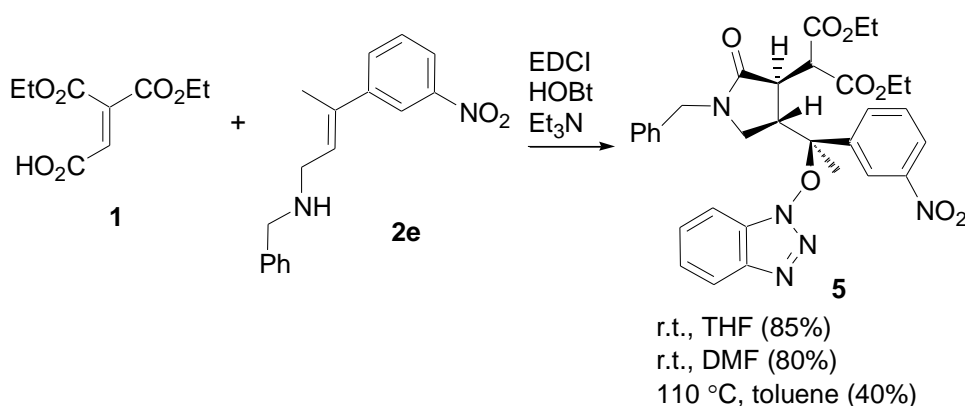

Scheme 6-3. Reaction of **1** and (*E*)-3-aryl-2-buten-1- amine **2e**.

The reaction of **1** and (*E*)-3-phenyl-3-bromo-2-propene-1-amine (*β*-bromo *cis*-cinnamylamine), **6** was examined next. Reaction of **1** and **6** with EDCI/HOBt/Et₃N at room temperature in THF or DMF gave the corresponding amide **7** in 48-75% yields as the isolable product. The reaction of **1** and **6** on heating at 80 °C gave *cis*-fused tricyclic compound **8** in 48% yield (Table 6-2).

Treatment of **7** with Et₃N or 1M HCl/EtOAc in benzene or toluene heating at 80-110 ºC gave *cis*-fused tricyclic compound **8** in 32-67% yields.

The stereochemistry of **8** was determined by observed NOEs. The observed *cis*-fused stereochemistry is in accord with that of *Z*-cinnmaylamine and C4 stereochemistry may arise from the protonation from less hindered side (*cis* to adjacent H), similar to the reactions of 3,3-diaryl-2-propen-1-amines.[6]

**Table 6-2.** Reactions of **1** and *(E)*-3-phenyl-3-bromo-2-propene-1-amine **7**.
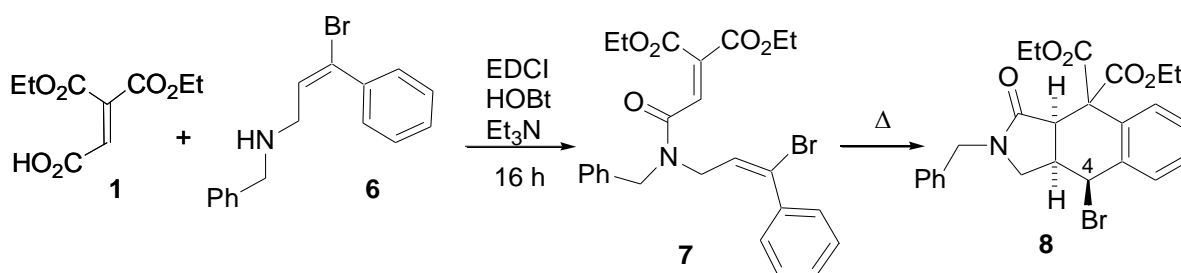
Entry	Starting Materials	Reagents	Solvent	Temp.	Product	Yield (%)
1	**1 + 6**	EDCI/HOBt/Et₃N	THF	r.t.	**7**	75
2	**1 + 6**	EDCI/HOBt/Et₃N	Benzene	80 °C	**8**	48
3	**7**	Et₃N (1 equiv.)	Benzene	80 °C	**8**	67
4	**7**	Et₃N (1 equiv.)	Toluene	110 °C	**8**	47
5	**7**	1M HCl/EtOAc (1 equiv)	Benzene	80 °C	a	
6	**7**		Benzene	80 °C	b	
7	**7**		DMF	80 °C	c	

ᵃ A mixture mainly containing **8**. ᵇ A mixture containing a small amount of **8**.
ᶜ A complex mixture.

In chapter 4, reaction of ethenetricalbocylate and *Z*-cinnamylamines at heating in the presence of EDCI/HOBt/Et₃N led *cis*-fused tricyclic compounds, and amide intermediate **A-*cis*** was not detected at room temperature.[6] The possible isolation of the amide **7** by lower reactivity than that of **A-*cis*** is probably due to both steric and electronic effects of Br group (Scheme 6-4).
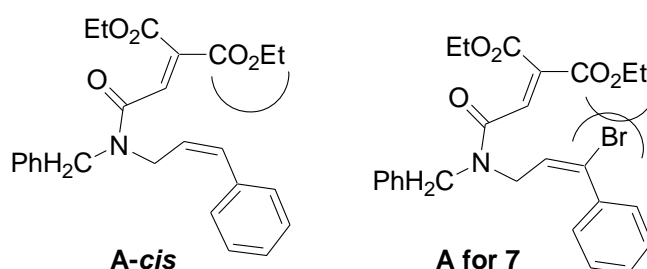
Scheme 6-4. Steric effects in [2 + 2] cycloaddition.

6-3 Conclusion

In summary, intramolecular cycloaddition reactions of β-substituted cinnamylamides of ethenetricarboxylate have been studied. Reaction of ethenetricarboxylic acid 1,1-diester and (*E*)-3-aryl-2-buten-1-amines with EDCI/HOBt/Et$_3$N led to pyrrolidine products in one pot, via intramolecular [2 + 2], [4 + 2] (IMDA) cycloadditions and HOBt-incorporated cyclization. The types of the products depend on the substituents on benzene ring, similarly to the reaction of *E*-cinnamylamines. Reaction of ethenetricarboxylic acid 1,1-diester and (*E*)-3-phenyl-3-bromo-2-propene-1-amine with EDCI/HOBt/Et$_3$N at room temperature gave the corresponding amide as an isolable product. Heating the amide with HCl or Et$_3$N gave a *cis*-fused tricyclic compound via [4 + 2] cycloaddition/H-transfer. Further study of the reaction of diversely substituted cinnamylamines and the corresponding amides under various conditions is in due course.

6-4 Experimental Section

General Procedures

[1]H Chemical shifts are reported in ppm relative to Me$_4$Si. [13]C Chemical shifts are reported in ppm relative to CDCl$_3$ (77.1 ppm). [13]C mutiplicities were determined by DEPT and HSQC. Peak assignments are made by 2D COSY, HSQC, NOESY, and HMBC spectra. Mass analyzer type used for EI is double-focusing in the HRMS measurements. Column chromatography was performed on silica gel (75-150 μm).

1,1-Diethyl 2-hydrogen ethenetricarboxylate **1** was prepared according to the literature.[7]

Arylpropenyl esters, ethyl (*E*)-3-phenylbut-2-enoate **Xa** (for **2a**), ethyl (*E*)-3-(4-methylphenyl)but-2-enoate **Xb** (for **2b**), ethyl (*E*)-3-(4-trifluoromethylphenyl)but-2-enoate **Xc** (for **2c**), ethyl (*E*)-3-(4-nitrophenyl)but-2-enoate **Xd** (for **2d**), ethyl (*E*)-3-(3-nitrophenyl)but-2-enoate **Xe** (for **2e**) and the corresponding alcohols, (*E*)-3-phenylbut-2-en-1-ol **Ya**, (*E*)-3-(4-methylphenyl)but-2-en-1-ol

Yb, (*E*)-3-(4-trifluoromethylphenyl)but-2-en-1-ol **Yc**, (*E*)-3-(4-nitrophenyl)but-2-en-1-ol **Yd**, and (*E*)-3-(3-nitrophenyl)but-2-en-1-ol **Ye** were prepared according to the literature.[8]

Ethyl (*E*)-3-(4-methylphenyl)but-2-enoate (Xb): (20 mmol scale, 3.8 g, 94%) R_f = 0.6 (hexane-EtOAc = 4 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.31 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 2.56 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.13 (s, 1H), 7.17 (d *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.38 (CH$_3$), 17.81 (CH$_3$), 21.21, (CH$_3$), 116.27 (CH), 126.23 (CH), 129.21 (CH), 139.15 (C), 139.224 (C), 155.45 (C), 167.02 (C), IR (neat) 2979, 1712, 1443 cm^{-1}, MS (EI) *m/z* 204 (M$^+$), HRMS (EI) *m/z* (M$^+$) 204.1152 (calcd for C$_{13}$H$_{16}$O$_2$ 204.1150)

Ethyl (*E*)-3-(4-trifluoromethylphenyl)but-2-enoate (Xc): (20 mmol scale, 4.8 g, 92%) R_f = 0.5 (hexane-EtOAc = 4 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.33 (t, *J* = 7.1 Hz, 3H), 2.58 (t, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 6.15 (s, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H) ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.30 (CH$_3$), 17.91 (CH$_3$), 60.14 (CH$_2$), 119.48 (CH), 126.68 (CH), 128.08 (CH), 130.49 (C), 145.83 (C), 153.80 (C), 166.44 (C), IR (neat) 2984, 1718, 1636, 1445, 1120 cm^{-1}, MS (EI) *m/z* 258 (M$^+$), HRMS (EI) *m/z* (M$^+$) 258.0867 (calcd for C$_{13}$H$_{13}$F$_3$O$_2$ 258.0868)

Ethyl (*E*)-3-(4-nitrophenyl)but-2-enoate (Xd): (20 mmol scale, 2.7 g, 57%) R_f = 0.5 (hexane-EtOAc = 4 : 1); colorless crystals; mp 71.5-72.5 °C (hexane-MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.33 (t, *J* = 7.1 Hz, 3H), 2.59 (s, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 7.27-7.64 (m, 2H), 8.22-8.26 (m, 2H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.34 (CH$_3$), 17.97 (CH$_3$), 60.36 (CH), 120.19 (CH), 123.86 (CH), 147.93 (CH), 152.76 (C), 166.17 (C), IR (KBr) 3117, 2987, 1717, 1517, 1182 cm^{-1}, MS (EI) *m/z* 235 (M$^+$), HRMS (EI) *m/z* (M$^+$) 235.0846 (calcd for C$_{12}$H$_{13}$NO$_4$ 235.0845)

Ethyl (*E*)-3-(3-nitrophenyl)but-2-enoate (Xe): (20 mmol, 3.8 g, 80%) R_f = 0.5 (hexane-EtOAc = 4 : 1); colorless crystals; mp 42.5-43.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.34 (t, *J* = 7.1 Hz, 3H), 2.61 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 6.21 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 10.5 Hz, 1H), 8.22 (d, *J* = 11.5 Hz, 1H), 8.33 (s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.35

(CH$_3$), 17.88 (CH$_3$), 60.33 (CH$_2$), 119.51 (CH), 121.35 (CH), 123.36 (CH), 129.66(CH), 132.24 (CH), 143.89 (C), 148.46 (C), 152.48 (C), 166.25 (C), IR (KBr) 2990, 1715, 1631, 1353, 1183 cm^{-1}, MS (EI) m/z 235 (M$^+$), HRMS (EI) m/z (M$^+$) 235.0847 (calcd for C$_{12}$H$_{13}$NO$_4$ 235.0845)

(*E*)-3-(4-Methylphenyl) but-2-en-1-ol (Yb): (1.2 mmol scale, 169 mg, 86%) colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.92 (bs, 1H), 2.04 (s, 3H), 2.3 (s, 3H), 5.47 (d, J = 5.5 Hz, 2H), 5.94 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 15.98 (CH$_3$), 21.08 (CH$_3$), 59.88 (CH$_2$), 125.64 (CH), 125.68 (CH), 128.67 (CH), 137.02 (C), 137.58 (C), 139.93 (C), IR (neat) 3341, 3024, 2921, 1647, 1512, 1444 cm^{-1}, MS (EI) m/z 162 (M$^+$), HRMS (EI) m/z (M$^+$) 162.1049 (calcd for C$_{11}$H$_{14}$O 162.1045)

(*E*)-3-(4-Trifluoromethylphenyl)but-2-en-1-ol (Yc): (12.8 mmol scale, 2713 mg, 98%) R$_f$ = 0.5 (hexane-EtOAc = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 2.11 (s, 3H), 2.21 (s, 1H), 6.4 (d, J = 6.4 Hz, 2H), 6.09 (t, J = 8.3 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 10.6 Hz, 1H), 8.09 (d, J = 10.0Hz, 1H), 8.23(s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 15.92 (CH$_3$), 59.77 (CH$_2$), 120.90 (CH) 121.96 (CH), 129.21 (CH), 129.32 (CH), 131.71 (CH), 135.23 (C), IR (neat) 3357, 2924, 1645, 1523, 1351, 1005 cm^{-1}, MS (EI) m/z 216 (M$^+$), HRMS (EI) m/z (M$^+$) 216.0760 (calcd for C$_{11}$H$_{11}$F$_3$O 216.0762) IR (neat) 3342, 3078, 2945, 1594, 1511, 1444 cm^{-1}, MS (EI) m/z 193 (M$^+$), HRMS (EI) m/z (M$^+$) 193.0736 (calcd for C$_{10}$H$_{11}$NO$_3$ 193.0739)

(*E*)-3-(4-Nitrophenyl)but-2-en-1-ol (Yd): (11 mmol scale, 2154 mg, 100%) pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm), 1.72 (s, 1H), 2.11 (s, 3H), 4.42 (d, J = 7.0, 2H), 6.11 (t, J = 7.7 Hz, 1H), 7.53-7.57 (m, 2H), 8.17-8.22 (m, 2H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 16.00 (CH$_3$), 59.98 (CH$_2$), 123.57 (CH), 123.72 (C), 123.82 (CH), 126.49 (CH), 130.51 (CH), 135.67 (C), 146.88 (C), 149.31 (C)

(*E*)-3-(3-Nitrophenyl)but-2-en-1-ol (Ye): (2.1 mmol scale, 406 mg, 94%) R$_f$ = 0.3 (hexane-EtOAc = 1 : 1); brown oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.90 (s,1H), 2.75 (s, 3H), 4.38 (d, J = 7.4 Hz, 2H), 6.02 (t, J = 8.5 Hz, 1H), 7.48 (d, J = 8.2Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 16.01 (CH$_3$), 59.91 (CH$_2$), 125.29 (CH), 129.45

(CH), 136.54 (C), 146.41 (C), IR (neat) 3358, 2929, 1654, 1411, 1113 cm^{-1}, MS (EI) m/z 193 (M$^+$), HRMS (EI) m/z (M$^+$) 193.0739 (calcd for C$_{10}$H$_{11}$NO$_3$ 193.0739)

The β-substituted cinnnamylamines, (E)-3-aryl-2-buten-1-amine (**2a-e**), (E)-3-aryl-3-bromo-2-propen-1-amine **6** were prepared from the corresponding alcohols, (E)-3-arylbut-2-en-1-ol(**Ya-e**), (E)-3-aryl-2-buten-1-amine. The corresponding bromides were prepared by reaction of the alcohols with PBr$_3$ in ether and used without further purification. The β-substituted cinnnamylamines **2a-e**, and **6** were prepared by reaction of benzylamine (2 equiv) with the corresponding bromids in ether according to the literature procedure.[9]

(E)-N-Benzyl-3-phenyl-2-buten-1-amine (2a): (2.8 mmol scale, 278 mg, 42%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.59 (bs, 1H), 2.03 (3, 3H), 3.46 (d, J = 7.4 Hz, 2H), 3.85 (s, 2H), 5.90 (t, J = 8.6 Hz, 1H), 7.21-7.41 (m, 10H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 16.17 (CH$_3$), 47.31 (CH$_2$), 53.63 (CH$_2$), 125.76 (CH), 126.50 (CH), 127.00 (CH), 127.06 (CH), 128.28 (CH), 128.50 (CH), 136.91 (C), 140.31 (C), 143.36(C), IR (neat) 3309, 3026, 1494, 1444 cm^{-1}, MS (EI) m/z 237 (M$^+$), HRMS (EI) m/z (M$^+$) 237.1510 (calcd for C$_{17}$H$_{19}$N 237.1517)

(E)-N-Benzyl-3-(4-methylphenyl)-2-buten-1-amine (2b): (12 mmol scale, 1.3 mg, 43%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 4); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.56 (s, 1H), 2.00 (s, 3H), 2.34 (s, 3H), 3.45 (d, J = 7.2 Hz, 2H), 3.84 (s, 2H), 5.88 (t, J = 8.8 Hz, 1H), 7.12, (d, J = 8.6 Hz, 2H), 7.24-7.34 (m 7H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 16.15 (CH$_3$), 21.11 (CH$_3$), 47.31 (CH$_2$), 53.63 (CH$_2$), 125.62 (CH), 127.25 (CH), 128.29 (CH), 128.49(CH), 128.96 (CH), 136.69 (C), 140.34 (C), 140.45 (C), IR (neat) 3025, 2918, 1512, 1494, 1452 cm^{-1} MS (EI) m/z 251 (M$^+$), HRMS (EI) m/z (M$^+$) 251.1676 (calcd for C$_{18}$H$_{21}$N 251.1674)

(E)-N-Benzyl-3-(4-trifluoromethylphenyl)-2-buten-1-amine (2c): (4.2 mmol scale, 582 mg, 45%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.67 (bs, 1H), , 2.02 (s, 3H), 3.46 (d, J = 6.6 Hz, 2H), 3.80 (s, 2H), 5.95 (t, J = 7.8 Hz, 1H), 7.22-7.27 (m, 1H), 7.30-7.34 (m, 4H), 7.46 (d, J = 9.6 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), ^{13}C NMR (100.6 MHz,

CDCl$_3$) δ (ppm) 16.01 (CH$_3$), 25.19 (CH$_2$), 53.58 (CH$_2$), 125.20 (CH), 125.24 (CH), 127.05(CH), 128.19 (CH), 128.51 (CH), 135.75 (C), 140.13(C), 146.81 (C), IR (neat) 3315, 3028, 2919, 1615, 1453 cm^{-1}, MS (EI) m/z 305 (M$^+$), HRMS (EI) m/z (M$^+$) 305.1387 (calcd for C$_{18}$H$_{18}$F$_3$N 305.1391)

(*E*)-*N*-Benzyl-3-(4-nitrophenyl)-2-buten-1-amine (2d): (6.8 mmol scale, 1.1 g, 57%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 4); blown oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.64 (s, 1H), 2.04 (s, 1H), 3.49 (d, J = 7.4 Hz, 2H), 3.85 (s, 2H), 6.05 (t, J = 7.2), 7.25-7.28 (m, 1H), 7.31-7.36 (m, 4H), 7.49 (d-like, J = 9.0 Hz, 2H), 8.14 (d-like, J = 9.0), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 15.87, (CH$_3$), 47.29 (CH$_2$), 53.68 (CH$_2$), 123.53 (CH), 126.22 (CH), 127.07 (CH), 128.15(CH), 128.32 (CH), 128.44 (CH), 130.69 (CH), 134.89 (C), 139.98 (C), 146.50 (C), 149.61 (C), IR (neat) 3027, 2840, 1593, 1513, 1453, 1344 cm^{-1}, MS (EI) m/z 282 (M$^+$), HRMS (EI) m/z (M$^+$) 282.1363 (calcd for C$_{17}$H$_{18}$N$_2$O$_2$ 282.1368)

(*E*)-*N*-Benzyl-3-(3-nitrophenyl)-2-buten-1-amine (2e): (10.3 mmol scale, 1.3 g, 56%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.69 (s, 1H), 2.50 (s, 3H), 3.48 (d, J = 6.4 Hz, 2H), 3.85 (s, 2H), 6.01 (t, J = 7.2 Hz, 1H), 7.23-7.29 (m, 1H), 7.31-7.40 (m, 2H), 7.44 (t, J = 7.9 Hz, 1H), 7.68 (d, J = 10.6 Hz, 1H), 8.05 (d, J = 10.6 Hz, 1H), 8.21 (s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 15.88 (CH$_3$), 47.21 (CH$_2$), 77.26 (CH$_2$), 120.43 (CH), 121.58 (CH), 127.02 (CH), 128.12 (CH), 128.41 (CH), 129.04 (CH), 129.27 (CH), 134.57 (CH), 134.57 (C), 140.00 (C), 144.76 (C), 148.26 (C), IR (neat) 3329, 3027, 2917, 2864, 2526, 1646, 1453 cm^{-1}, MS (EI) m/z 282 (M$^+$), HRMS (EI) m/z (M$^+$) 282.1359 (calcd for C$_{17}$H$_{18}$N$_2$O$_2$ 282.1368)

(*E*)-3-Phenyl-3-bromo-2-propen-1-amine (6): (1.8 mmol scale, 320 mg, 69%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.65 (bs, 1H), 3.23 (d, J = 7.3 Hz, 2H) 3.70 (s, 1H) 6.35 (t, J = 7.1 Hz, 1H), 7.20-7.33 (m, 10H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 48.33 (CH$_2$), 53.10 (CH$_2$), 123.11 (C), 127.12 (CH), 128.18 (CH), 128.25 (CH), 128.34 (CH), 128.46 (CH), 128.53 (CH), 128.77 (CH), 128.94 (CH), 132.72 (CH), 138.28 (CH), 139.78 (C), IR (neat) 3028, 2838, 1636 cm^{-1}, MS (CI) m/z 302 (M$^+$), 304 ([M+H]$^+$); HRMS (CI) m/z [M+H]$^+$ 302.0541, 304.0525 (calcd for C$_{16}$H$_{17}$BrN 302.0544, 304.0524)

Typical experimental procedure for preparation of 3, 4, 5, 7, and 8 (Scheme 6-2). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF_3CO_2H (4 mL))[7] in DMF (0.8 mL) were added (*E*)-3-aryl-2-buten-1-amine (**2a**) (237 mg, 1 mmol) in DMF (0.8 mL), Et_3N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2.2 mmol), and EDCI (1-[3-(dimethylamino)- propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2 M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexane-EtOAc to give **3a** (214 mg, 49%).

3a: R_f = 0.8 (hexane-EtOAc = 1 : 4); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.30 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.33 (s, 3H), 2.85-2.89 (m, 1H), 3.04 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.31 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.72 (d, *J* = 8.2 Hz, 1H), 4.13-4.33 (m, 4H), 4.37 (d, *J* = 20.4 Hz, 1H), 4.47 (d, *J* = 14.4 Hz, 1H), 7.25-7.38 (m, 10H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 14.42 (CH$_3$), 15.02 (CH$_3$), 21.29 (CH$_3$), 39.44 (CH), 39.79 (CH), 45.38 (CH$_2$), 46.71 (CH$_2$), 59.81 (CH$_2$), 64.53 (CH$_2$), 79.56 (C), 82.58 (C), 125.04 (CH), 127.82 (CH), 128.22 (CH), 128.73 (CH), 136.04 (C), 142.66 (C), 161.30 (C), 166.73 (C), 172.59 (C), IR (neat) 3061, 2982, 1698, 1620, 1495, 1444, 1262 cm^{-1}, MS (EI) *m/z* 435 (M$^+$), HRMS (EI) *m/z* (M$^+$) 435.2047 (calcd for $C_{26}H_{29}NO_5$ 435.2046)

4c-ax: R_f = 0.5 (hexane-EtOAc = 1 : 1); colorless crystals; mp 156.0-157.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.21 (t, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 4.5 Hz, 3H), 1.27 (t, *J* = 8.6 Hz, 3H), 2.70-2.79 (m, 1H), 3.17-3.32 (m, 4H), 4.08-4.16 (m, 1H), 4.23-4.48 (m, 5H), 4.77 (d, *J* = 15.0 Hz, 1H), 7.26-7.37 (m, 7H), 7.51 (d, *J* = 1.4, 1H), 7.66 (s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.79 (CH$_3$),14.07 (CH$_3$), 18.53 (CH$_3$), 34.69 (CH), 35.43 (CH) 43.90 (CH$_2$) 46.55 (CH$_2$), 46.60 (CH$_2$), 62.26 (CH$_2$), 62.81 (CH$_2$), 124.80 (CH), 127.61 (CH), 127.92 (CH), 128.21 (CH),

128.73 (CH), 130.62 (CH), 134.25 (C) 136.68 (C), 146.03 (C), 157.80 (C), 167.85 (C), 170.23 (C), 171.63 (C), IR (KBr) 2983, 1745, 1685, 1437, 1258, 1116 cm^{-1}, MS (EI) m/z 503 (M$^+$), HRMS (EI) m/z (M$^+$) 503.1923 (calcd for C$_{27}$H$_{28}$F$_3$N$_5$O$_5$ 503.1920)

4d-eq: (0.5 mmol scale, DMF, 110 °C, 147 mg, 60%) R$_f$ = 0.2 (hexane-EtOAc = 1 : 1); colorless crystals; mp 165.0-166.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) 1.26 (t, J = 7.1 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 2.14-2.25 (m, 1H), 2.93-3.01 (m, 1H), 3.04-3.11 (m, 3H), 3.52 (t, J = 8.4, 1H), 4.12-4.20 (m, 1H), 4.30-4.52 (m, 5H), 4.68 (d, J = 14.8 Hz, 1H), 7.27-7.51 (m, 5H), 7.50 (d, J = 8.8 Hz, 1H), 8.13 (dd, J = 8.7, 2.4), 8.27 (d, J = 2.5 Hz, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.92 (CH$_3$), 14.13 (CH$_3$), 18.77 (CH$_3$), 38.94 (CH), 39.15 (CH), 46.54 (CH$_2$), 49.45 (CH), 49.63 (CH$_2$), 60.97 (CH$_2$), 62.55 (CH$_2$), 63.17 (CH$_2$), 122.95 (CH), 125.95 (CH), 127.72 (CH), 128.23 (CH), 128.56 (CH), 128.82 (CH), 136.01 (C), 136.49 (C), 146.35 (C), 148.25 (C), 167.71 (C), 167.00 (C), 171.31 (C), IR (KBr) 3110, 3002, 1737, 1677, 1609, 1517, 1517, 1433, 1253 cm^{-1}, MS (EI) m/z 480 (M$^+$), HRMS (EI) m/z (M$^+$) 480.1900 (calcd for C$_{26}$H$_{28}$N$_2$O$_7$ 480.1897)

5: R$_f$ = 0.4 (hexane-EtOAc = 1 : 1); colorless crystals; mp 148.0-149.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.17 (t, J = 5.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.49 (s, 3H), 3.18 (t, J = 4.5 Hz, 1H), 3.33-3.38 (m, 1H), 3.49-3.53 (m, 1H), 3.66-3.71 (m, 2H), 3.86-3.94 (m, 1H), 4.06-4.23 (m, 4H), 4.72 (d, J = 14.5 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.22-7.24 (m, 2H), 7.28-7.35 (m, 4H), 7.42 (t, J = 8.1 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.33 (s, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.89 (CH$_3$), 13.94 (CH$_3$), 18.79 (CH$_3$), 43.58 (CH), 43.90 (CH), 46.99 (CH$_2$), 47.03 (CH$_2$), 52.18 (CH), 61.84 (CH$_2$), 61.94 (CH$_2$), 93.87 (C), 108.77 (CH), 120.32 (CH), 122.28 (CH), 124.01 (CH), 124. 74 (CH), 127.93 (CH), 128.53 (CH), 128.62 (CH), 128.76 (CH), 129.61 (CH), 133.44 (CH), 135.48 (C), 141.44 (C) 142.55 (C), 167.56 (C), 167.80 (C), 171.68 (C), IR (KBr) 2991, 1736, 1685, 1530, 1489, 1442, 1269, 1023 cm^{-1}, MS (EI) m/z 615 (M$^+$), HRMS (EI) m/z (M$^+$) 615.2327 (calcd for C$_{32}$H$_{33}$N$_5$O$_8$ 615.2329)

7: R_f = 0.6 (hexane-EtOAc = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers, ratio 1:1) δ (ppm) 1.29, (t, J = 7.1 Hz, 3H×0.5), 1.30 (t, J = 7.1 Hz, 3H×0.5), 1.32 (t, J = 7.1 Hz, 3H×0.5), 1.37 (t, J = 7.1 Hz, 3H×0.5), 3.80 (d, J = 7.0 Hz, 2H×0.5), 3.93 (d, J = 7.0 Hz, 2H×0.5), 4.24-4.41 (m, 4H+2H×0.5), 4.52 (s, 2H×0.5), 6.16 (t, J =7.0 Hz, 1H×0.5), 6.22 (t, J = 7.0 Hz, 1H×0.5), 6.91-6.94 (m, 2H×0.5), 6.99 (m, 2H×0.5), 7.19-7.35 (m, 9H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.97 (CH$_3$), 14.04 (CH$_3$), 14.06 (CH$_3$), 14.09 (CH$_3$), 44.20 (CH$_2$), 46.49 (CH$_2$), 47.96 (CH$_2$), 62.01 (CH$_2$), 62.07 (CH$_2$), 62.23 (CH$_2$), 62.29 (CH$_2$), 125.10 (CH), 125.63 (CH), 127.23 (CH), 127.23 (CH), 127.76 (CH), 128.10 (CH), 128.17 (CH), 128.29 (CH), 128.41(CH), 128.52 (CH), 128.63 (CH), 128.73 (CH), 128.83 (CH), 128.85 (CH), 128.89 (CH), 129.04 (CH), 129.40 (CH), 134.25 (CH), 134.66 (C), 134.90 (CH), 135.16 (C), 135.37 (C), 137.22 (C), 137.61 (C), 162.80 (C), 162.89 (C), 164,16(C), 164.23 (C), 164.293 (C), 164.33(C), IR (neat) 2982, 1731, 1650, 1443, 1255, 1204 cm^{-1}, MS (EI) m/z 499, 501 (M$^+$), HRMS (EI) m/z (M$^+$) 499.0994, 501.0973 (calcd for C$_{25}$H$_{26}$BrNO$_5$ 499.0994, 501.0974)

8: (1 mmol scale, benzene, 80 °C, 242 mg, 48%) R_f = 0.4 (hexane-EtOAc = 1 : 1); pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.13 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 3.11-3.18 (m, 1H), 3.22 (t, J = 8.4 Hz, 1H), 3.61 (d, J = 11.9 Hz, 1H), 3.66 (t, J = 8.9 Hz, 1H), 3.98-4.06 (m, 1H), 4.17-4.23 (m, 1H), 4.26 (d, J = 14.7 Hz, 1H), 4.38-4.52 (m, 1H), 4.79 (d, J = 9.8 Hz, 1H), 4.82 (d, J = 14.7 Hz, 1H), 7.25-7.36 (m, 9H), 7.68-7.71 (m, 1H), ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.70 (CH$_3$), 13.98 (CH$_3$), 40.28 (CH), 46.96 (CH$_2$), 48.29 (CH), 52.03 (CH$_2$), 52.57 (CH), 60.79 (C), 62.19 (CH$_2$), 62.68 (CH$_2$), 127.48 (CH), 127.56 (CH), 128.31 (CH), 128.36 (CH), 128.45 (CH), 128.57 (CH), 128.69 (CH), 134.36 (C), 134.54 (C), 136.02 (C), 168.66 (C), 169.44 (C), 171.83 (C), IR (neat) 2980, 1731, 1640, 1445, 1260 cm^{-1}, MS (EI) m/z 499, 501 (M$^+$), HRMS (EI) m/z (M$^+$) 499.0990, 501.978 (calcd for C$_{25}$H$_{26}$BrNO$_5$ 499.0994, 501.0974)

Transformation of 7 to 8 (Table 6-5, entry 5). To a solution of **7** (483 mg, 0.97 mmol) in benzene (2 mL) was added Et$_3$N (0.135 mL, 99 mg, 0.97 mmol). The mixture was stirred at 80 °C for 16 h.

The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane-Et$_2$O to give **8** (324 mg, 67%)

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Chapter 7
Conclusion

In this research, sequential amide formation/cyclization reaction of substituent arylpropenylamine and ethenetricarboxylate was investigated.

In chapter 2, the reaction of furylamines and ethenetricarboxylate with sequential amide formation/intramolecular Diels-Alder (IMDA) reaction at room temperature, was studied. Amide intermediates were not detected.

In chapter 3, intramolecular [2 + 2] and [4 + 2] cycloaddition (IMDA) reactions of cinnamylamides and ethenetricarboxylate in sequential processes were studied. Diversity of the reaction pattern depending on the substituents of the benzene ring was formed. Reaction of cinnamylamines without substituents on the benzene ring and with halogens and OMe on para positions at room temperature gave cyclobutane-fused pyrrolidines as the major products via [2 + 2] cycloaddition. Reaction of ethenetricarboxylate and cinnamylamines bearing electron-withdrawing groups such as NO_2, CN, CO_2Me, CO_2Et, or CF_3 on ortho and para positions in the presence of EDCI/HOBt/Et$_3$N at room temperature or at 60−80 °C gave tetrahydrobenz[*f*]isoindolines via IMDA reaction as the major products.

In chapter 4, IMDA reactions of various 3,3-diarylpropenylamides of electron-deficient alkenes to give hexahydrobenzo[*f*]isoindoles stereoselectively were studied. Reaction of ethenetricarboxylate with 3,3-diaryl-2-propen-1-amines under the amide formation conditions gave the tricyclic compounds in sequential processes involving IMDA reaction. The reaction gave *cis*- and *trans*-fused tricyclic compounds selectively, depending on the substituents on the benzene ring, reaction temperature, and solvent. In the reaction with dissymmetrically substituted 3,3-diaryl-2-propen-1-amines, *trans*-substituted aryl group reacted mainly as a styrene component. Amides of electron-deficient alkenic carboxylic acids such as fumarate do not

undergo cyclization at room temperature sequentially and the reaction on heating gave *trans*-fused hexahydrobenzo[*f*]isoindoles.

In chapter 5, the reaction of ethenetricarboxylate with (heteroaryl)propenylamine was studied. Reaction of ethenetricarboxylate with (*E*)-3-(2-furyl)-2-propen-1-amines in the presence of EDCl/HOBt/Et$_3$N at 80-110 °C gave *cis*-fused tricyclic compounds as major products. On the other hand, reaction with (*E*)-3-(3-furyl)-2-propen-1-amines at 80-110 °C gave *trans*-fused tricyclic compounds as major products. The reaction of 3-(3-pyridinyl)-2-propen-1-amine gave HOBt-incorporated pyrrolidine diastereoselectively.

In chapter 6, the reaction of 3-aryl-2-butenylamines with ettenetricarboxylate was developed stereoselectively. Reaction of (*E*)-3-aryl-2-buten-1-amine without substituents on the benzene ring at room temperature gave cyclobutane-fused pyrrolidine as the major product via [2 + 2] cycloaddition. Reaction of (*E*)-3-aryl-2-buten-1-amine bearing *p*-NO$_2$ and *p*-CF$_3$ on benzene ring in the presence of EDCI/HOBt/Et$_3$N at room temperature or at 110 °C gave tetrahydrobenz-[*f*]isoindolines via IMDA reaction as the major products stereoselectively. Reaction of (*E*)-3-phenyl-3-bromo-2-propen-1-amine under the amide formation conditions at room temperature gave non-cyclized amide. The amide was transformed to *cis*-fused tricyclic compound in the presence of acid or base on heating.

In this thesis, the efficient and chemoselective synthesis of cyclized products in the reaction of electron-deficient alkenyl carboxylates such ethenetricarboxyate with various arylpropenylamines was developed. The new synthetic methods of the multicyclic compounds are expected to be useful in the development of new highly functional materials.

List of Publications

1. Inter- and Intramolecular Diels-Alder Reaction of Ethenetricarboxylate Derivatives

    S. Yamazaki, H. Sugiura, M. Niina, Y. Mikata, A. Ogawa, *Heterocycles*. **2016**, 92, 3, 485

    (Chapter 2)

2. Intramolecular [2 + 2] and [4 + 2] Cycloaddition Reactions of Cinnamylamides of Ethenetricarboxylate in Sequential Processes

    S. Yamazaki, H. Sugiura, S. Ohashi, K. Ishizuka, R. Saimu, Y. Mikata, A. Ogawa, *J. Org. Chem.* **2016**, 81, 22, 10863

    (Chapter 3, Chapter 6)

3. Intramolecular Cyclization of 3,3-Diarylpropenylamides of Electron-deficient Alkenes: Stereoselective Synthesis of Functionalized Hexahydrobenzo[*f*]isoindoles

    H. Sugiura, S. Yamazaki, K. Go, A. Ogawa, *Eur. J. Org. Chem.* doi/abs/10.1002/ejoc.201801508

    (Chapter 4, Chapter 6)

4. Sequential Intramolecular Diels-Alder Reaction of 3-Heteroaryl-2-propenylamides of Ethenetricarboxylate

    H. Sugiura, S. Yamazaki, A. Ogawa, Submitted to *J. Heterocycl. Chem.*

    (Chapter 5, Chapter 6)

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